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NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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ASSOCIATION OF AMERICAN PHYSICIANS

OFFICERS FOR THE YEAR 1917–1918

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ALEXANDER McPHEDRAN, M.D.

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REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS

RICHARD P. STRONG, M.D.

ALTERNATE REPRESENTATIVE

FRANCIS W. PEABODY, M.D.

ASSOCIATION OF AMERICAN PHYSICIANS

OFFICERS FOR THE YEAR 1918-1919

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CHARLES F. MARTIN, M.D.

REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS

RICHARD P. STRONG, M.D.

ALTERNATE REPRESENTATIVE

FRANCIS W. PEABODY, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis A. Delafield	.....	.....	James Tyson.	A. B. Ball
1887.	S. Weir Mitchell.	Francis Minot. / R. Palmer Howard.	J. T. Whittaker.	G. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. / R. Palmer Howard	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. / S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. / Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1907.	F. P. Kinnicutt.	James Tyson.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1909.	V. C. Vaughan.	Henry Hun.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1913.	L. F. Barker.	Simon Flexner.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1914.	Simon Flexner.	S. J. Meltzer.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1915.	S. J. Meltzer.	Henry Sewall.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1916.	Henry Sewall.	George Dock.	Thomas McCrae.	Geo. M. Kober.	J. P. C. Griffith.
1917.	George Dock.	F. H. Williams.	T. R. Boggs.	T. McCrae.	J. P. C. Griffith.
1918.	F. H. Williams.	Alex. McPhedran.	T. R. Boggs.	T. McCrae.	Joseph A. Capps.
1919.	Alex. McPhedran.	Herman M. Biggs.	W. W. Ford.	T. McCrae.	Joseph A. Capps.

ACTIVE MEMBERS

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Johns Hopkins Medical School, Baltimore, Md.
1894. Adami, J. George, Pathological Laboratory, McGill University, Montreal, Canada.
1905. Adams, Samuel S., 1801 Connecticut Ave., Washington, D. C.
1918. Allen, F. M., Rockefeller Institute, 66th St. and Ave. A., New York.
1911. Anders, James M., 1605 Walnut St., Philadelphia.
1913. Anderson, John F., 195 College Ave., New Brunswick, N. J.
1911. Ashford, Bailey K., U. S. Army, San Juan, P. R.
1913. Auer, John, Rockefeller Institute, 66th St. and Ave. A, New York.
1908. Baldwin, E. R., Saranac Lake, N. Y.
1899. Barker, L. F., 1035 North Calvert St., Baltimore, Maryland.
1916. Bass, Charles C., Tulane Univ., New Orleans.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 122 S. Michigan Blvd., Chicago.
1901. Blumer, George, 204 York St., New Haven, Conn.
1913. Boggs, Thomas R., 21 West Chase St., Baltimore, Md.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1915. Brill, Nathan E., 48 W. 76th St., New York.
1913. Brooks, Harlow, 5 West 9th St., New York.
1911. Brown, Lawrason, 104 Main St., Saranac Lake, N. Y.
1904. Brown, Philip K., 516 Sutter St., San Francisco, Cal.
1914. Brown, Thomas R., 19 W. Biddle St., Baltimore.
1918. Brown, W. H., Rockefeller Institute, 66th St. and Ave. A., New York.
1913. Bunting, C. H., University of Wisconsin, Madison.
1899. Cabot, R. C., 1 Marlborough St., Boston.
1912. Camac, C. N. B., 128 E. 60th St., New York.
1914. Cannon, Walter B., Harvard Medical School, Boston.
1908. Capps, Joseph A., 150 Michigan Ave., Chicago.
1907. Christian, Henry A., 252 Marlborough St., Boston.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.
1917. Cohn, Alfred E., 315 Central Park West, New York.
1909. Cole, Rufus I., 960 Park Ave., New York.

ELECTED

1914. Coleman, Warren, 58 West 55th St., New York.
1904. Collins, Joseph, 37 West 54th St., New York.
1908. Conner, Lewis A., 121 East 62d St., New York.
1906. Coplin, W. M. L., 606 South 48th St., Philadelphia.
1917. Dochez, Alphonse R., Rockefeller Institute, 66th St. and Ave. A, New York.
1893. Dock, George, 600 S. Kingshighway, St. Louis, Missouri.
1904. Edsall, David L., 80 Marlborough St., Boston, Mass.
1901. Edwards, Arthur R., 104 S. Michigan Ave., Chicago.
1915. Emerson, Charles P., Medical School, University of Indiana, Indianapolis.
1918. Emerson, Haven, 120 E. 62d St., New York.
1915. Erlanger, Joseph, 600 S. Kingshighway, St. Louis.
1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
1916. Foster, Nellis B., University Hospital, Ann Arbor, Mich.
1908. Freeman, R. G., 211 W. 57th St., New York.
1913. Friedenwald, Julius, 1013 N. Charles St., Baltimore, Md.
1917. Frothingham, Jr., Channing, 395 Marlborough St., Boston.
1918. Fulton, F. T., 273 Bowen St., Providence, R. I.
1894. Fussell, M. Howard, 421 Lyceum Ave., Manayunk, Phila.
1903. Futcher, Thomas B., 23 West Franklin St., Baltimore.
1914. Gay, Frederick P., University of California, Berkeley.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1908. Hamilton, W. F., 287 Mountain St., Montreal, Canada.
1915. Hamman, Louis V., 714 Park Ave., Baltimore.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1918. Hart, T. S., 160 W. 59th St., New York.
1918. Heard, J. D., 6101 Penn Ave., Pittsburgh, Pa.
1898. Herrick, James B., People's Gas Building, Chicago.
1910. Hewlett, Albion W., Stanford Med. School, San Francisco, Cal.
1911. Hoover, C. F., 702 Rose Building, Cleveland, Ohio.
1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., 1213 N. Calvert St., Baltimore.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
1916. Hunt, J. Ramsay, 20 W. 50th St., New York.
1907. Hunt, Reid, Harvard Med. School, Boston.

ELECTED

1917. Irons, Ernest E., 122 S. Michigan Ave., Chicago.
1901. Jackson, Henry, 380 Marlborough St., Boston.
1916. Jobling, James W., Vanderbilt Univ., Nashville, Tenn.
1902. Joslin, E. P., 81 Bay State Road, Boston.
1916. Karsner, Howard T., Lakeside Hospital, Cleveland.
1901. Kinyoun, J. J., 1421 Clifton St., Washington, D. C.
1915. Klotz, Oskar, University of Pittsburgh, Pittsburgh.
1900. Koplik, Henry, 30 East 62d St., New York.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1915. Landis, H. R. M., 11 S. 21st St., Philadelphia.
1917. Lee, Roger I., Harvard Medical School, Boston.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
1910. Libman, E., 180 East 64th St., New York.
1912. Locke, Edwin A., 311 Beacon St., Boston.
1911. Loeb, Leo, 600 S. Kingshighway, St. Louis.
1909. Longcope, Warfield T., 41 E. 70th St., New York.
1910. Lord, Frederick T., 305 Beacon St., Boston.
1905. McCrae, Thomas, 1627 Spruce St., Philadelphia.
1891. McPhedran, A., 151 Bloor St. W., Toronto, Canada.
1902. MacCallum, W. G., The Hopkins Hospital, Baltimore.
1905. Macallum, A. B., Ottawa, Canada.
1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1892. Meltzer, S. J., 13 West 121st St., New York.
1905. Meyer, Adolph, Johns Hopkins Medical School, Baltimore.
1917. Miller, James A., 379 Park Ave., New York.
1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
1908. Moffitt, Herbert C., 240 Stockton St., San Francisco, Cal.
1915. Morris, Roger S., Cincinnati General Hospital, Cincinnati.
1917. Mosenthal, Herman O., The Hopkins Hospital, Baltimore.
1915. Noguchi, Hideyo, Rockefeller Institute, 66th St. and Ave. A, New York.
1914. Norris, Geo. W., 1530 Locust Street, Philadelphia.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
1918. Ordway, T., Albany Medical College, Albany, N. Y.
1899. Park, Wm. H., 315 West 76th St., New York.
1916. Peabody, Francis W., Peter Bent Brigham Hospital, Boston.
1904. Pearce, R. M., Medical School, Univ. of Penna., Philadelphia.
1918. Piersol, George Morris, 1913 Spruce St., Philadelphia, Pa.
1918. Plummer, H. S., Mayo Clinic, Rochester, Minn.
1909. Pratt, Joseph H., 317 Marlborough St., Boston.
1899. Prince, Morton, 458 Beacon St., Boston.
1894. Rachford, B. K., 1961 Madison Rd., Cincinnati.

ELECTED

1904. Richardson, Mark W., 67 Milk St., Boston.
1905. Riesman, David, 1715 Spruce St., Philadelphia.
1915. Robinson, G. Canby, 600 S. Kingshighway, St. Louis.
1907. Rosenau, M. J., Harvard Medical School, Boston, Mass.
1916. Rous, Peyton, 131 E. 19th St., New York.
1915. Rowntree, Leonard G., Univ. of Minn., Minneapolis.
1911. Rudolf, Robert D., 396 Bloor St. W., Toronto, Canada.
1911. Russell, Frederick F., Surgeon-General's Office, U. S. Army, Washington, D. C.
1898. Sachs, B., 116 W. 59th St., New York.
1908. Sailer, Joseph, 1718 Spruce St., Philadelphia.
1900. Sewall, Henry, 1360 Vine St., Denver, Col.
1902. Sippy, B. W., 122 S. Michigan Avenue, Chicago, Ill.
1892. Smith, Theobald B., Princeton, N. J.
1907. Sollmann, Torald H., 1353 E. 9th St., Cleveland, Ohio.
1915. Southard, Elmer E., 74 Fenwood Road, Boston.
1916. Steiner, Walter R., 646 Asylum Ave., Hartford, Conn.
1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1911. Strong, R. P., Harvard Medical School, Boston.
1917. Swift, Homer F., 65 Central Park West, New York.
1916. Taussig, Albert E., Metropolitan Bldg., St. Louis.
1907. Taylor, A. E., University of Pennsylvania, Philadelphia.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 61 W. 49th St., New York.
1912. Tileston, Wilder, 424 Temple St., New Haven.
1914. Wadsworth, Aug. B., 278 Yates St., Albany.
1901. Warthin, Aldred S., Univ. of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 1743 W. Harrison St., Chicago.
1918. Webb, G. B., Colorado Springs, Colo.
1912. Wells, H. G., Sprague Memorial Institute, Chicago.
1913. Whipple, Geo. H., Hooper Foundation, University of California Hospital, San Francisco, California.
1917. White, Franklin W., 322 Marlborough St., Boston.
1918. White, S. M., Donaldson Bldg., Minneapolis, Minn.
1915. White, Wm. Charles, 2851 Bedford Ave., Pittsburgh.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1918. Wolbach, S. B., Harvard Medical School, Boston, Mass.
1917. Wood, Edward J., 201 Chestnut St., Wilmington, N. C.
1914. Wood, Francis C., 437 W. 59th St., New York.
1916. Woodyatt, Rollin T., 104 S. Michigan Ave., Chicago.

ASSOCIATE MEMBERS

ELECTED

1917. Addis, Thomas, Lane Hospital, San Francisco.
1917. Austin, J. H., Univ. Hospital, Philadelphia.
1918. Draper, G., 116 E. 63d St., New York.
1916. Edmunds, Charles W., Univ. of Michigan, Ann Arbor, Mich.
1915. Einhorn, Max, 20 E. 63d St., New York.
1918. Evans, J. S., University of Wisconsin, Madison, Wis.
1916. Eyster, John H., Univ. of Wisconsin, Madison, Wis.
1918. Fitz, R., Rockefeller Institute, 66th St. and Ave. A. New York.
1918. Giffin, H. Z., Mayo Clinic, Rochester, Minn.
1917. Hamburger, W. W., 104 S. Michigan Ave., Chicago.
1917. Hess, A. F., 16 W. 86th St., New York.
1916. Hirschfelder, Arthur D., Univ. of Minnesota, Minneapolis.
1917. Krumbhaar, E. B., Med. Dept., Univ. of Pa., Philadelphia.
1917. Lewis, P. A., Phipps Institute, Philadephia, Pa.
1916. Loevenhart, Arthur S., Univ. of Wisconsin, Madison, Wis.
1917. Meakins, J. C., 392 Mountain St., Montreal.
1918. Musser, John H., 338 S. 21st St., Philadelphia, Pa.
1917. Newburgh, L. H., Univ. Hospital, Ann Arbor.
1914. Pemberton, Ralph, 2224 Locust St., Philadelphia.
1918. Rehfuss, M. E., 16th and Spruce Sts., Philadelphia, Pa.
1916. Rosenow, Edward C., Mayo Clinic, Rochester, Minn.
1917. Sellards, A. W., Harvard Med. School, Boston.
1916. Shattuck, George C., 135 Marlborough St., Boston.
1914. Smith, Elsworth, Humboldt Building, St. Louis.
1917. Warfield, L. M., 79 Wisconsin St., Milwaukee.

HONORARY MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED HONORARY MEMBER	
	1916.	Gorgas, William C., Surgeon-General, U. S. A., Washington, D. C.
*1886.	1915.	Hun, Henry, 149 Washington Ave., Albany.
*1886.	1912.	Jacobi, A., 19 East 47th St., New York.
1902.	1916.	Kober, Geo. M., 1819 Q St., N. W., Washington.
*1886.	1912.	Osler, Wm., 13 Norham Gardens, Oxford, England.
*1886.	1913.	Prudden, T. Mitchell, 160 W. 59th St., New York.
*1886.	1915.	Tyson, James, 1506 Spruce St., Philadelphia.
1889.	1915.	Vaughan, Victor C., Univ. of Michigan, Ann Arbor.
*1886.	1913.	Welch, William H., 807 St. Paul St., Baltimore.

EMERITUS MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1905.	1918.	Babcock, R. H., 74 East Elm St., Chicago.
1898.	1916.	Blackader, A. D., 236 Mountain St., Montreal.
1892.	1916.	Bolton, Meade B., Charlottesville, Va.
1898.	1917.	Brannan, John W., 48 W. 51st St., New York.
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
1889.	1916.	Cary, Charles, 340 Delaware Ave., Buffalo.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1897.	1905.	Cushny, Arthur C., University of London, London, England.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1888.	1916.	Dana, Charles L., 53 W. 53d St., New York.
*1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A. Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, 637 S. Wood St., Chicago.
*1886.	1908.	Henry, Frederick P., 114 S. 18th St., Philadelphia
1900.	1917.	Holt, L. E., 14 W. 55th St., New York.
1890.	1902.	Hurd, H. M. Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1895.	1918.	Lafleur, H. A., 215 Peel St., Montreal, Canada.
1898.	1916.	Mallory, F. B., Harvard Medical School, Boston.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1901.	1913.	Morse, John L., 70 Bay State Road, Boston.
1891.	1918.	Northrup, W. P., 61 E. 73d St., New York.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
1903.	1918.	Puble, R. B., 590 Dearborn Ave., Chicago.
*1886.	1915.	Putnam, James J., 106 Marlborough St., Boston.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
*1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Phila.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
1899.	1918.	Thacher, J. S., 20 W. 50th St., New York.
1898.	1918.	Vickery, H. F., Ipswich, Mass.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.
1898.	1915.	Wesbrook, F. F., Univ. British Columbia, Vancouver, B. C.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
*1886.	1908.	Wood, Horatio C, 4107 Chester Ave., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members

DATE OF ELECTION

1896. Adler, Isaac, New York.
*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Delafield, Francis A., New York.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
1899. Ely, John Slade, New Haven, Conn.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
*1886. Graham, J. E., Toronto, Canada.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, Jr., E. Darwin, New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Janeway, E. G., New York.
1908. Janeway, T. C., Baltimore.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.

DATE OF ELECTION

1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
*1886. McBride, Thomas A., New York.
1914. McCrae, John, Montreal, Canada.
1890. MacDonnell, R. P., Montreal, Canada.
1887. Meigs, Arthur V., Philadelphia.
*1886. Metcalfe, John T., Cold Springs, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1898. Mitchell, John K., Philadelphia.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.
*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Sinkler, Wharton, Philadelphia.
*1886. Smith, A. A., New York.
1891. Smith, Andrew H., New York.
1905. Steele, J. Dutton, Philadelphia.
*1886. Sternberg, Geo. M., Washington.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
1889. Thomson, W. H., New York.
*1886. Trudeau, Edward L., Saranac Lake.
*1886. Ward, Samuel B., Albany.
*1886. Whittaker, James T., Cincinnati.
*1886. Wilkins, George, Montreal.
1898. Withington, Charles F., Boston.

ASSOCIATION

OF

AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 10, 1916

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to one hundred and sixty. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members, without regard to the length of his previous active membership.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the

Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the *Transactions* as also in any other medical publication.

5. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution twenty-five members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the

nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTY-THIRD ANNUAL MEETING

Held at the Hotel Traymore, Atlantic City, N. J., May 7 and 8, 1918

The following members were present at the meeting:

Allen, F. M.
Auer, John
Barker, L. F.
Bass, Charles C.
Biggs, Herman M.
Blumer, George
Brill, Nathan E.
Brooks, Harlow
Brown, Thomas R.
Camac, C. N. B.
Christian, Henry A.
Cohen, Solomon Solis
Cole, Rufus I.
Coleman, Warren
Coplin, W. M. L.
Dock, George
Einhorn, Max
Emerson, Charles P.
Flexner, Simon
Ford, W. W.
Foster, Nellis B.
Freeman, R. G.
Friedenwald, Julius
Fussell, M. Howard
Futcher, Thomas B.
Gordinier, H. C.
Hamman, Louis V.
Herrick, James B.
Hess, A. F.
Hoover, C. F.
Howard, W. T.
Hun, Henry
Hunt, J. Ramsay
Hunt, Reid
Jacobi, A.
Joslin, E. P.
Karsner, Howard T.
Klotz, Oskar
Kober, George M.
Koplik, Henry
Lambert, Samuel M.
Landis, H. R. M.
Lewis, P. A.
Libman, E.
Locke, Edwin A.
McCrae, Thomas
McPhedran, A.
Meltzer, S. J.
Mosenthal, Herman O.
Opie, E. L.
Park, Wm. H.
Plummer, H. S.
Prudden, T. Mitchell
Richardson, Mark W.
Riesman, David
Rous, Peyton
Russell, Frederick F.
Sachs, B.
Sippy, B. W.
Smith, Elsworth
Southard, Elmer E.
Steiner, Walter R.
Stengel, Alfred
Stockton, Charles G.
Taussig, Albert E.
Tileston, Wilder
Wadsworth, Aug. B.
Welch, William H.
White, Franklin W.
Williams, Francis H.
Wolbach, S. Burt
Wood, Edward J.
Wood, Francis C.

Active Members—F. M. Allen, New York; W. H. Brown, New York; H. Emerson, New York; F. T. Fulton, Providence; T. S. Hart, New York; J. D. Heard, Pittsburgh; T. Ordway, Albany; G. M. Piersol, Philadelphia; H. S. Plummer, Rochester; G. B. Webb, Colorado Springs; S. M. White, Minneapolis; S. B. Wolbach, Boston.

Associate Members—G. Draper, New York; J. S. Evans, Madison; R. Fitz, New York; H. Z. Giffin, Rochester; M. E. Rehfuss, Philadelphia; J. H. Musser, Philadelphia.

Dr. J. B. Herrick presented a paper on "Thrombosis of the Coronary Artery," which was discussed by Drs. Dock, Meltzer, Libman and Christian, and the discussion was closed by Dr. Herrick.

Papers were presented by Dr. S. Flexner on "The Serum Treatment of Meningitis," by Dr. W. W. Herrick on "Intravenous Serum Treatment of Cerebrospinal Meningitis," and by Dr. H. L. Amoss on "The Essential Properties of a Potent Antimeningococcic Serum." These papers were discussed by Drs. Park, Koplik, Meltzer, Barker, Libman, Wadsworth, and the discussion closed by Drs. Flexner and Herrick.

Dr. L. F. Barker presented a paper on "Myrtol and Eucalyptol Poisoning," which was discussed by Dr. Flexner.

Drs. J. Friedenwald, and F. H. Baetjer presented a paper on "Clinical Aspects of Peptic Ulcer, with Special Reference to Roentgen-ray Diagnosis," which was discussed by Drs. Barker, Brown and Sippy, and the discussion closed by Dr. Baetjer.

Dr. B. W. Sippy presented a paper on "The Healing of Peptic Ulcer," which was discussed by Dr. Friedenwald.

Dr. H. O. Mosenthal presented a paper on "The Comparative Food Value of Protein, Fat and Alcohol in Diabetes Mellitus as Measured by the Nitrogen Equilibrium."

Dr. George Dock presented a paper on "A Case of Bulimia, with Remarks on the Casual Treatment of Some Functional Diseases," which was discussed by Drs. Barker and Coleman, and the discussion closed by Dr. Dock.

Dr. M. Einhorn presented a paper on "The Fractional Examination of the Duodenal Contents."

Wednesday Afternoon, May 8

Dr. H. T. Karsner presented a paper on "The Relation of War Wounds to Acute Endocarditis," which was discussed by Drs. Ford and McCrae.

Dr. E. L. Opie presented a paper on "Investigation of Trench Fever Carried out in Northern France," which was discussed by Dr. Futcher, and the discussion closed by Dr. Opie.

Dr. R. I. Cole presented a paper on "Pneumonia in the Army Camps," and Dr. C. N. B. Camac on "The Serum Treatment of Pneumonia (Lobar)," which were discussed by Drs. Joslin, Brooks, Wadsworth, Russell, Herrick (W. W.), and Cole, and the discussion closed by Dr. Camac.

Dr. A. F. Hess presented a paper on "Antiscorbutics and Intravenous Therapy for Scurvy."

Mr. E. C. Kendall presented a paper on "The Thyroid Hormone and its Relation to Metabolism."

Dr. T. R. Brown presented a paper on "Studies on Some Unusual Types of Diarrhea," which was discussed by Dr. Plummer.

Dr. D. Riesman presented a paper on "Remarks on Chronic Septicemic Endocarditis with Splenomegaly: its Treatment by Splenectomy," which was discussed by Dr. Libman.

Dr. E. E. Southard presented a paper on "The General Theory of Clinical Diagnosis, with Special Reference to the Application of a Key Principle to Major Groups of Mental Disease," which was discussed by Drs. Barker and Dock, and the discussion closed by Dr. Southard.

Dr. J. R. Hunt presented a paper on "Clinical Types of Paralysis Referable to the Pallidal System of the Corpus Striatum," which was discussed by Dr. Southard.

Dr. E. S. Smith presented a paper on "Some Preliminary Observations on Certain Phases of Hypertension," which was discussed by Drs. Plummer and Dock, and the discussion closed by Dr. Plummer.

Dr. H. S. Plummer presented a paper on "The Function of the Thyroid Gland," which was discussed by Drs. Barker and Dock.

The papers of Dr. A. B. Wadsworth on "A Study of the Endocardial Lesions Developing during Pneumococcus Immunization in Horses"; Dr. S. S. Cohen on "Three Unusual Cases of Low Thoracic Aneurysm, Simulating Pleural Effusion, with Two Autopsies"; Drs. J. J. Abel and C. A. Rouiller on "In What Form Are Protein Digestion Products Taken Up by the Mucosa of the Stomach and Intestines"? and Drs. J. Howland and W. M. Marriott on "Observations upon the Mineral Equilibrium of the Blood Plasma," were read by title.

On the motion of Dr. Barker, seconded by Dr. Dock, a vote of thanks was given to Dr. Williams for the very interesting program of the meeting and for the able way in which he had administered his term of office.

THOMAS MCCRAE, M.D.,
Secretary.

ADDRESS OF THE PRESIDENT

THE IMPORTANCE OF BEDSIDE INSTRUCTION IN THE TEACHING OF THERAPEUTICS

By FRANCIS H. WILLIAMS, M.D.
BOSTON

We have to record our loss during the past year of one emeritus member, Dr. William Hanna Thomson; three active members, Dr. Isaac Adler, Dr. Theodore Caldwell Janeway, and Dr. John McCrae; and one associate member, Dr. Richard Weil. Dr. Janeway and Dr. Weil died in the Service here, and Dr. John McCrae in the Service abroad.

I am sure the Association would desire to have the following poem by Dr. John McCrae become a part of our transactions, and I therefore include it.

IN FLANDERS FIELDS

In Flanders fields the poppies blow
Between the crosses, row on row
That mark our place; and in the sky
The larks, still bravely singing, fly
Scarce heard amid the guns below.

We are the Dead. Short days ago
We lived, felt dawn, saw sunset glow,
Loved and were loved, and now we lie
In Flanders fields.

Take up our quarrel with the foe;
To you from failing hands we throw
The torch; be yours to hold it high,
If ye break faith with us who die,
We shall not sleep, though poppies grow
In Flanders fields.

Allow me to express my appreciation of the double honor you have conferred upon me, first in electing me to membership in this Association, and second in entrusting to me the duties of President for the year; both imply that I should bring a suggestion to this meeting. Permit me, then, to direct your thoughts toward some questions relating to instruction in treatment: Cannot patients and practitioners derive more benefit from our present knowledge of pharmacology and therapeutics? Are there not some things known to older practitioners which are not brought home to students in lectures or even in clinical exercises, and others known to pharmacologists which are not carried so fully and minutely into practice as to achieve all that might be accomplished? It is not necessary for me to recall to your minds the many difficulties which the young practitioner has to encounter and overcome in his attempts to unravel and adapt to practice the complexity of pharmacological and therapeutic detail which has been presented to him in different years of his medical course.

There is, I believe, a gap between the instruction given in materia medica, pharmacology and therapeutics on the one hand and the requirements of medical practice on the other, which, were it filled, would assist in making therapeutics even more valuable than at present. Let me recall to your minds the detailed instruction given to students in the comparatively few things employed in the surgical treatment of patients. An example of this is afforded by the instruction in the use of splints and bandages. The students are not only taught in a general way how and why these are used, but must apply them repeatedly, and the work is done in small sections. Students should be trained in a similar manner in the medical treatment of patients. The power in the hands of the physician does not display itself so dramatically as that in the hands of the surgeon, but it is no less essential, and opportunities for its use are more frequent.

Not only must a subject so unusually complex as therapeutics be presented in lectures and recitations, but also more opportunity should be afforded for bedside instruction, given by a physician who has had a training in pharmacology, as well as a clinical experience. To illustrate what I mean by bedside instruction, let me

describe some exercises of the character I would advocate, which I gave about thirty years ago: The students were taken into the wards in small sections, not exceeding eight in number, and standing about the patient's bed were given the diagnosis, together with a brief outline of the case. They were then told to consider that the patient had come to them for treatment, and, after any questions which they wished to ask had been answered, were required to write, on blocks of paper which had been distributed to the section, what they would do if the patient were their own. This was not limited to the use of remedies, but included directions as to diet, occupation, habits of life, etc. These outlines were handed to the instructor, and as some were ready sooner than others, there was sufficient time for him to look over each paper without delaying the exercise. The papers usually fell into three groups: One in which the students had done well; another in which they had outlined a treatment which was incomplete; and a third in which they had made serious mistakes, for example, in choosing the wrong remedies, in giving them in an amount or in a way which would fail to be of any value, or in such a way or such an amount that harm might be done. Comments were made freely by the instructor, so that all got the benefit of what was good as well as the warning involved in the mistakes made. As names were not mentioned, the comments were impersonal and could thus be made more emphatic. A most convincing evidence of the need of instruction of this nature was afforded by the character of many of the answers written at these exercises. After the students had done their best, and had been told why some of their directions should not be followed, they had an opportunity to see how the physician met the situation. At subsequent visits the results of treatment could be noted.

In these exercises the instructor, when prescribing a laxative, a hypnotic, or an analgesic, for example, was able to recall briefly to the minds of the students the important members of the group from which it was chosen, and give the reasons for his choice, why it was especially adapted to the patient's condition, and the precautions which should be taken to promote success and avoid harm. In order to emphasize still further the clinical side, the final examination in therapeutics included not only the usual written examination,

but also an oral examination, which gave a better opportunity to bring out the proficiency of the students on this side of the subject.

In connection with the exercises described above, but in larger sections, the students had two or three others in which they were shown how a hot-air bath should be given, methods of administering remedies, of feeding, etc., and also some demonstrations by trained nurses. A young practitioner recently confided to me his perplexity when, as a house officer, he was told to give a patient a hot-air bath; he had never seen it done and did not know how to go about it. For a medical student to have an opportunity to see such demonstrations once, with explanations, is sufficient.

This method of instruction, namely, requiring each student of a small group at the bedside to state what he considers the proper treatment for the patient, under the oversight of an experienced physician who has had a training in pharmacology, is not used in our medical schools, so far as I can judge from the catalogues of more than twenty of our best schools. Incidentally, I noted that in more than one-half of these there was no professor of therapeutics. This subject is one of the most important in the course, and every medical school should have, I believe, such a professor, who should be in touch with all instruction concerning medical treatment in the school.

Let me quote here a sentence from a statement made about thirty years ago, as a result of my experience with this method of instruction, a copy of which I came across recently:

"I believe that bedside teaching of therapeutics is of the first importance to students, to practitioners, and to the community; that no other method is so well adapted to show students how the obstacles in the way of giving relief to patients are to be overcome, or to have the practitioner know how to distinguish between what is of service to the patient and what is harmful, to have him appreciate the dangers of new or absurd methods of treatment, and understand how to carry out safely and advantageously the many means of relief which are at our command, and of which it is sometimes very culpable for the practitioner to be ignorant."

This method gives the student an opportunity to realize the limi-

tations of treatment, to appreciate the need of judgment and courage to use a powerful remedy in such amounts and in such a way as the occasion demands, and to gain a sense of values, that is, to see the problem of treatment in perspective, a difficult thing for many minds to acquire in any subject. It also offers another opportunity for joining the experimental method which prevails in the laboratories of chemistry, physiology and pharmacology, with the observational method for which the clinic affords such wide scope and leads the student to form habits of thought which make him a better practitioner, and more truly a professional man.

In lectures it is impossible to present the subject of therapeutics in a manner suited to the minds of all members of a large class; probably only a minority of them are reached. On the other hand, with small sections, at the bedside, the instructor comes in contact with the individual student and his difficulties, and may thus appreciate what he has failed to grasp.

It is an advantage to have the bridge, which connects the teaching of therapeutics with its application in practice, built and used in the medical school, where the student can have assistance in this difficult task rather than that unaided he should attempt its construction out of what he has heard in his lectures and recitations on the one hand, and his clinical inexperience on the other.

My plea is for a careful, painstaking rehearsal at the bedside by the student of what he is to do as a practitioner. Let him first be trained without taking responsibility, and when the time comes this training will help him to give a good account of himself in his fight against disease, and to choose and carry out the proper measures.

He who can give sleep by simpler means than hypnotics, or can relieve many of the lesser forms of pain without resorting to morphin, has obtained a more complete command of therapeutic resources than one who uses the more powerful remedies to overcome the lesser obstacles. He who can accomplish his results in the simplest way is, as always, the artist, past master of his art.

As we look back over the history of medicine, we see that the attitude of the physician toward disease and what he can do to relieve and eliminate it has changed from generation to generation, as our knowledge of the sciences has advanced. Medical students

should be made to realize that the role of the practitioner is to assist nature, and that, though nature, as a rule, must do most of the work, she frequently needs the aid which a wise physician can render today in greater degree than ever before, and without which she would often be helpless.

To picture the opportunities which will be in the hands of the practitioner of the future, even within two or three generations, is inspiring; it will then be a still greater privilege to be a physician.

The following letter reached the President shortly after the meeting: The delay was due perhaps to its having passed through the hands of the censor:

"From the Regius Professor of Medicine, Oxford,

April 18, 1918.

Dear Williams:

How I wish I could be at the meeting, but it is impossible. The Association remains very dear to my heart, and among my most precious memories are those happy early days of close fellowship with Mitchell and Draper, Delafield, Jacobi, Fitz, Pepper and others. The hopes of the founders have been fully realized in the splendid work the Association has done for the profession. Tell the younger men for me to live in the spirit of Delafield's address to us at the first meeting. . .

With love to you all,

Yours sincerely,

Wm. Osler."

RESULTS FROM THE INTRAVENOUS USE OF SALVARSAN IN SYPHILIS OF THE NERVOUS SYSTEM

By B. SACHS, M.D.
NEW YORK

At this critical period of our national life it seems especially important to consider carefully the various methods of treatment of a disease that maims so often and so rarely kills. Those of us who during several decades have had unusual opportunities of studying syphilis of the nervous system realize a great responsibility in the matter of putting before the entire medical profession correct views regarding various methods of treatment that have been proposed. A year ago I felt impelled to expound what I believed to be "The Truth about Intraspinal Injections in Syphilis of the Nervous System." It is very evident that to some "The Truth" was not altogether palatable. I am more firmly convinced than ever of the correctness of my views, and in a publication by Drs. Strauss and Kaliski[1] a careful critical analysis of over 400 cases from my service was given.

Let me state briefly why we pinned our faith to the intravenous use of salvarsan, neosalvarsan or arsphenamin, and why we are ready to reject the more dangerous intraspinous method of treatment.

This entire subject concerns not only the neurologists and the dermatologists: it concerns even to a greater degree the general medical practitioner. Among dermatologists, Dr. Fordyce has seen fit to reply to my article of last year. I am most anxious to avoid all personal controversy; the subject is so far more important than the personages involved that it would be a grievous error to allow this controversy to descend to the plane of charges and recriminations.

[1] Syphilis of the Nervous System, American Journal of Syphilis, October, 1918.

Dr. Fordyce writes that "if the statements contained in that [my] article are accepted by the medical profession as a final and correct judgment of this new therapeutic procedure (meaning intraspinous injections) an enormous amount of harm will result in that numerous victims of syphilis of the nervous system will be deprived of their only chance to regain health and economic efficiency." Far from depriving them of their only chance for recovery, I believe that by advocating the intravenous treatment no lives will be lost, no unnecessary paralyses will result from treatment and far less harm will be done by the innumerable number of medical men who will be called upon to treat syphilis of the nervous system than if the intraspinous method were to be generally adopted and heralded as the only method of efficiency in the treatment of syphilis of the nervous system. It is because the intravenous method, which hundreds of physicians have already learned to administer skilfully if energetically pursued, will bring about results comparable with those obtained in the treatment of early specific lesions involving other organs, that I believe that much more good will be accomplished if there is the slightest suspicion that syphilis has invaded the nervous system, if physicians and surgeons give the intravenous treatment and do not necessarily wait until they can find someone skilful enough to administer the intraspinous injections.

Again, Dr. Fordyce implies there was in my article an attempt to discredit the value of serological examinations of the spinal fluid as a diagnostic measure and guide to treatment. Such an accusation is entirely unfounded, and in my hospital service all laboratory tests are utilized to the fullest extent possible. My point of view is and has been simply this: Serological examinations and all the biological tests are of the greatest possible value as corroborative evidence. I am not willing, however, to allow that clinical evidence is to be entirely superseded or disregarded. So many of the physicians engaged in these researches seem to forget that negative findings, serologically and biologically, do not disprove the presence of syphilis as a causative factor of disease. Wassermann himself, in his earliest articles and in all others that have come to my notice, has never departed from this original statement of his. In our own experience we have again and again, on clinical evidence, and in the

absence of positive findings, given intravenous treatment when our own experience has taught us that certain groups of symptoms could only be explained on the assumption of syphilis, and in no other way. Moreover, I must adhere to the views previously expressed that there is no actual correspondence between the serological findings in certain cases of syphilis of the nervous system and the progress of the underlying morbid process. In general paresis we have, possibly as a result of energetic treatment, seen the most marked remissions without any tangible change in the serological findings. The same is true of tabes and is invariably true of the spastic group of syphilitic disease of the spinal cord. On the other hand, we have entire lists of cases in which the serological findings show remarkable changes after intravenous injections, after repeated lumbar punctures, without corresponding improvement or deterioration in the clinical symptoms. It is only in the group of the more distinctly specific meningeal disorders and meningo-encephalitic disorders and in some of the vascular group that the serological findings and the clinical symptoms seem to progress or to deteriorate *pari passu*.

Taking up this subject somewhat more in detail, my associates and myself have endeavored to discover why the intraspinous treatment did not yield the results expected of it and why intravenous treatment in reality accomplished much more than we had a right to anticipate. Although my friend Dr. Fordyce waives aside all attempts at theory by assuring us that his patients have been cured and relieved by intraspinous treatment when intravenous treatment had failed, and that they would smile at the thought that successful treatment was theoretically impossible, I believe it not amiss to state once more a few fundamental facts regarding the limitations of the intraspinous treatment of syphilis of the nervous system. I grant that, in view of the excellent results obtained in the acute infectious disorders of the central nervous system and recorded by Flexner and his associates, the thought was entirely natural that similar results should be obtained in syphilitic disease. But there is a vast difference between the acute infectious disorders and the more chronic syphilitic disease dependent upon the difference in the manner of invasion in the toxic products formed and in the

final habitat of the respective microörganisms. In general paresis and in tabes the chief lesions are within the substance of the brain or of the cord far removed from actual contact with the cerebrospinal fluid. It is for that reason almost impossible to bring the spirocheticidal remedy into immediate contact with the foci of disease unless these remedies can be introduced through the blood streams. It is only in the earliest stages of tabes dorsalis that the disease, as we have long since known, involves the meninges and the spinal ganglia; later on it sets up marked degenerative changes in the spinal tissue, and these secondary changes are entirely beyond the reach of the cerebrospinal fluid and its contents. In the remaining meningo-encephalitic and meningomyelitic processes of specific origin, more or less exudative in character, we would suppose that spirocheticidal substances introduced in the cerebrospinal fluid might have an active therapeutic effect if such substances could course freely in the cerebrospinal fluid, and if it could be shown that they were retained in this fluid for any satisfactory period of time. Let me refer here once more to the fact that four years ago, with the assistance of Professor Benedict, we succeeded in showing that salvarsan introduced in the usual quantities into the blood current appeared in the cerebrospinal fluid in appreciable quantities. In this way we refuted the doctrine of the impermeability of the choroid plexus and that salvarsan introduced intravenously could not be expected to exert any influence over the cerebral and spinal tissues. The question, therefore, narrowed itself practically to this: Whether or not as much spirocheticidal substances, say salvarsan, reached the cerebrospinal canal in intravenous treatment, as it was safe to introduce directly into the cerebrospinal fluid by lumbar puncture.

I appreciate the ingenious methods which have been elaborated by Ravaut, by Swift and Ellis and by Ogilvie, but further studies on the functions and the behavior of the cerebrospinal fluid seemed to have made these methods more or less superfluous. It will not do to disregard the studies of Weed, a pupil of Cushing, who pointed out that the pressure in the cerebral capillaries is considerably higher than the cerebrospinal tension, and that it is far more likely that fluid leaves the cerebral capillaries and circulates in the capillary and perineuronal spaces yielding nourishment and receiving

waste products, and finally leaving the tissues by the pericapillary and perivascular spaces to the subarachnoid cavities over the surface whence absorption into the venous sinuses takes place. The natural inference of these various studies is that a metallic substance like salvarsan introduced into the spinal canal is rapidly absorbed into the venous system, and if this be true, why not utilize the venous system at once for the conveyance of these metallic substances rather than the roundabout route *via* the cerebrospinal fluid. It has also been shown that the cerebrospinal fluid circulates imperfectly and that there is very little absorption of this fluid by the cortical or spinal cells.

However attractive the intraspinous medication has appeared to be, it is essentially useless and theoretically unsound. British authors, among them Halliburton, have abandoned the use of salcarsan in locomotor ataxia and similar late syphilitic affections *via* the cerebrospinal fluid, because they claim it is fatal not only to the syphilitic organism but also to the patient. There is some satisfaction, also, in noting that Major Swift, in an article written abroad, now concedes that he never contended that intraspinal treatment alone was the best or the ideal treatment of syphilis of the nervous system, and I am firmly convinced that men like Swift, who surely appreciate physiological evidence, will grant that thus far the argument is against intraspinous and in favor of intravenous treatment.

There is still another reason why we have been practically compelled to adopt the intravenous method exclusively in the treatment of syphilitic disease of the central nervous system, Dreyfuss was, perhaps, the first to insist upon the frequent repetition and the large doses of salvarsan to be used in these disorders What his present-day views are we have no means of knowing. Starting out with that suggestion, we have in my own service become more and more convinced of the value of intensive treatment, especially in the earlier and remedial stages of cerebral and spinal syphilitic disease. We have obtained most satisfactory results from intravenous injections administered on alternate days for a period of three or four weeks according to the symptoms presented by the patient and then allowing a period of complete rest or giving weekly or semiweekly injections of salicylate of mercury for a period of

four to six weeks and then again starting in with the same course of salvarsan injections. Some of our patients have received as many as forty to fifty intravenous injections within a period of twelve to eighteen months. There may be a few men who could with impunity give the same number of intraspinal injections, but the patient will certainly be none the better for them, and even the most skilful of the intraspinous injectionists have had disagreeable experiences to record. Personally, I regard the lumbar puncture as a more or less innocuous procedure provided fluid only is withdrawn, but I have too much respect for the cerebrospinal content to sanction innumerable injections of toxic substances into the canal.

The medical profession is entitled to know what the actual results are from the use of intravenous medication. Let me summarize my beliefs by stating first that no other specific medication has ever been as satisfactory as has been the intravenous use of salvarsan. Wherever there is good reason to suspect that the symptoms of nervous disease are due to the specific poison, the antisyphilitic medication should be begun as early as possible and persisted in as long as possible. The very best results will, no doubt, be obtained in those cases in which the anatomical pathological lesion is relatively slight and young. In the cases of intense headaches, probably meningeal, in some of the earliest forms of specific optic neuritis, in the large number of cases of cerebrospinal lues with actual nerve palsies with moderate paralytic symptoms, with incomplete vesical disturbance, in the victims of vascular disease, in arteritis luetica, and, above all, in a rather important group of syphilitic epilepsies, intensive intravenous treatment leads not infrequently to a cure and very often to a marked improvement in all the symptoms. But in this group of cases it is easy for us to realize that the morbid process is largely confined to the meninges and to the surface of the cortical or spinal tissue, but the spirochete can no doubt be reached through vascular channels. A group of purely spastic palsies with very slight sensory changes, with little or no vesical disturbance, with much more rigidity than paralysis, the group which Erb so well described and which is long since recognized as a purely degenerative group, yields least to intravenous or to any other form of antisyphilitic medication. The question of the effective treatment is

most in doubt when we come to consider the results in locomotor ataxia. And here you will pardon me for saying that only those who have had a vast experience in the observation of tabes are able to speak with any sort of authority. The tabetic pains, the crises, the bladder symptoms and the sexual impotence, which Fordyce especially advances in his effort to prove that he is curing his patients of tabes by the intraspinous method—all these conditions may be relieved by antisyphilitic medication as we have known them to be relieved by prolonged periods of rest, by hydrotherapeutic procedures, by mercurial injections, by almost any other method of treatment that has from time to time been advocated for the treatment of tabes dorsalis. My own impression, based upon the large number of cases that we have had under treatment is that the early and persistent use of salvarsan intravenously administered makes the entire course of the disease far less progressive than it was formerly wont to be. It is no exaggeration to state that in innumerable cases we appeared to check the progress of the disease. It has been a special source of chagrin to me, therefore, to note the rapid deterioration of symptoms in some of the cases of locomotor ataxia that have done extremely well upon intravenous treatment, and upon intraspinous medication administered by others and not by us, have developed paralytic symptoms and absolute impairment of the vesical function when there was no reason whatever to expect these symptoms to be superadded to the many others. Aside from this no one can claim that he has actually brought about a single and definite cure in an undoubted case of tabes dorsalis. There are cases of lues cerebrospinalis that simulate tabes as there are others that simulate general paresis in which there may be a return of the knee-jerk or even a change in the pupillary immobility, particularly in the earlier stages, subsequent to the introduction of salvarsan into the system; but in a full-fledged case of tabes dorsalis no one has even been able to record the actual disappearance of the classic symptoms of the disease. Very much the same that we have said regarding tabes dorsalis might be said regarding general paresis, except that there is in the case of general paresis the added difficulty of estimating the value of any form of medication because of the natural remissions of the disease. The sober judgment

based upon sufficient experience might lead the therapeutic enthusiast to claim that the remissions are longer than they used to be, that the disease lasts longer than it did in former years. I would not contradict the truth of such statements in a disease so grave as general paresis: It is my ambition to remain optimistic so long as there is the slightest encouragement. Moreover, there is in the earliest period of a very large number of cases of general paresis a reasonable doubt as to the actual disease, and we speak of these cases as being doubtful as to whether they are genuine general paresis or whether they are pseudoparesis which nine times out of ten means nothing else than that in some instances the luetic disease may remain restricted to the meninges and to the superficial layers of the cortex, whereas in other cases the disease makes further inroads into the cortical tissue and the spirochete find their ultimate and permanent resting places within the substance of the brain. So long, however, as there is any doubt regarding the actual development of the disease it is the duty of everyone, particularly in the earliest stages of the disease, to give the most intensive form of intravenous treatment and only to desist when the progress of the symptoms has been such that it is certain that the disease will have to run the usual unfavorable course.

The chief practical deduction from these experiences is that the most intensive intravenous treatment should be given as soon as possible after the initial specific infection has been established. Without reference especially to the nervous system, let the most intensive treatment be given so as to avoid later complications. From the frequency with which pupillary immobility can be recognized as the only clinical symptom of constitutional lues, I am inclined to think that the nervous system is more often involved in constitutional lues than it is generally suspected to be. In spite of the fact that we have observed, particularly in youthful and again in senile individuals, the very early development of syphilitic disease of the central nervous system in spite of intensive intravenous medication, it is well to urge, as a measure of safety, that the intravenous medication of salvarsan cannot be begun too early if the ravages of the disease are to be minimized. The future of the success of antisyphilitic therapy lies in the hope that the profession

at large will persist in this form of treatment in every case of syphilitic infection for a number of years after the initial lesion. And so far as the interests of society at large are concerned, there is a crying need, especially in our large cities, for the adequate intravenous treatment of all patients with the initial syphilitic lesions. Such patients should unquestionably be kept under absolute medical control for a number of years. Further hope lies in the ultimate discovery of a substance less toxic than salvarsan, which in even larger quantities could be introduced and safely introduced into the circulation.

THE RELATION BETWEEN THE CHEMICAL STRUCTURE OF THE OPIUM ALKALOIDS AND THEIR ACTION ON SMOOTH MUSCLE

AND CONCERNING THE PHARMACOLOGICAL AND THERAPEUTIC PROPERTIES OF SOME BENZYL ESTERS

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During the past four years the author has been engaged in an extensive and intensive pharmacological study of opium, and more especially of the so-called "minor" opium alkaloids, individually and in combination with each other and with the principal opium alkaloid—morphin. As the result of that work, it soon became evident that the minor opium alkaloids can be regarded as "minor" only in respect to their small quantitative content in crude opium, but not in respect to their pharmacological action. Indeed, it was shown that these alkaloids can and do modify the effects of morphin very markedly when given in combination with it. Thus it was pointed out that there is a distinct difference in the analgesic effect produced by morphin, on the one hand, and by opium, on the other, due to the presence of the minor alkaloids in the latter.[1] Again, important differences have been shown to exist for the same reason between the pharmacological action of morphin and opium on the respiratory center,[2] the vomiting center[3] and other centers in the medulla.

One interesting feature disclosed by the pharmacological studies just mentioned is the fact that while opium and its alkaloids exert their most marked effects on the central nervous system, nevertheless they produce also distinct and important pharmacological

effects on peripheral structures, and more particularly on smooth muscle organs. The action of the opium alkaloids on smooth muscle was first studied by the author in connection with a pharmacological study of the ureter, because excised rings of that organ permit of an accurate analysis of the action of drugs on the rhythmic contractions or peristaltic movements and the tonicity of smooth muscle.[4] It was soon established from studies on the excised ureters of lower animals and of man, as well as from observations of the ureters in lower animals *in situ*, that the opium alkaloids in respect to their action on that organ can be divided sharply into two classes: the pyridin-phenanthrene group, of which morphin is the principal member, on the one hand, and the benzyl-isoquinolin group, of which papaverin is the principal representative, on the other. The morphin group was found to stimulate the contractions of the ureteral preparations and increase their tonicity, while all the members of the papaverin group were found to inhibit the contractions of the ureter and lower its tonus.

It was found, furthermore, that in combinations of members of the two groups small amounts of the benzyl-isoquinolin class were sufficient to overcome the stimulating effects of the morphin group. These observations led to several practical deductions. Thus, at the suggestion of the author, Dr. J. T. Geraghty injected a solution of papaverin directly into the ureter of a patient and in that way facilitated the expulsion of a small ureteral calculus.[5] Again, the tonus-lowering action of papaverin and its relatives gives a scientific explanation to the well-known empirical observation that opium is more efficient in relieving the pains of renal colic than is morphin when given alone, because when administering the combination of total opium alkaloids the patient has the advantage of both the central narcotic or analgesic effect of morphin as well as the peripheral tonus-lowering or antispasmodic influence of the papaverin group.[6]

Following the studies of the effects of the opium alkaloids upon the smooth muscle of the ureter, the author investigated the action of the same alkaloids upon other kinds of smooth muscle. The results of these investigations have in part already been published[7 8] and in part are to appear later. The smooth muscle struc-

tures thus studied were the following: Intestine, pyloric rings, uterus, gall-bladder, urinary bladder, biliary ducts, seminal vesicles, vas deferens, bronchial rings, and rings of excised arteries. As a result of these investigations the author was led to conclude that the action of the opium alkaloids upon all kinds of smooth muscle structures is the same as that described in connection with the ureter, namely, that the morphin alkaloids *stimulate* contractions and *increase* tonus while the papaverin alkaloids *inhibit* contractions and *lower* tonicity, and, furthermore, that so far as the peripheral effect is concerned, in case of combinations of the two groups, the benzyl-isoquinolin constituents exert the predominating effect. Here, again, some practical deductions were drawn from the experimental data. Thus it was found, as has been long known by empirical observation, that opium is more efficient in relieving gall-stone colic and uterine colic than is morphin when administered alone.[9]

Following the experimental investigations just described, the author undertook a further analysis of the interesting peripheral action of the opium alkaloids on smooth muscle. The results of these investigations have been published elsewhere.[10] Briefly stated the conclusions to which these studies have led were that the stimulating effect of the pyridin-phenanthrene group of alkaloids is to be attributed to the *pyridin* portion of their molecules, while the inhibitory and tonus-lowering action of papaverin and the other members of the benzyl-isoquinolin group were to be ascribed to the presence of the *benzyl* grouping in their molecules. The reasons for these conclusions are to be found explained in detail elsewhere.

These observations and conclusions led the author to surmise that possibly the inhibitory and tonus-lowering effect of papaverin might be produced by the exhibition of a benzyl grouping in a simpler form. Accordingly a search was made for simple non-alkaloidal and non-narcotic compounds containing the benzyl radical which could be administered to animals without toxic results. Two such bodies were discovered. They are the well-known esters, *benzyl-benzoate* and *benzyl-acetate*. Inasmuch as these esters are practically insoluble in water, their pharmacological action could not be well studied on excised tissues or isolated organs, but experiments

with them on intact animals revealed the fact that both of these esters actually produced the same pharmacological effects as those given by the opium alkaloid papaverin on the one hand, and that these esters were much less toxic than papaverin on the other.[11] Metabolic studies in connection with these experiments showed that the benzyl group of benzyl-benzoate and benzyl-acetate is, in a large measure, converted in the body into hippuric acid and is excreted as such in the urine. The comparatively very low toxicity of benzyl-benzoate and benzyl-acetate for animals and their striking papaverin-like effects on various viscera led the author to try their action upon himself, and as no untoward or even disagreeable symptoms followed the ingestion of these drugs by mouth it was deemed justifiable to administer these agents to suitable patients with their consent.

The conditions in which the benzyl effect was anticipated to produce therapeutic results were those exhibiting either *excessive peristalsis* or excessive *spasm* of smooth muscle. It would take too much time in this preliminary communication to describe in detail all the cases in which the benzyl esters were administered. The author need only state that for oral administration the benzoate was chiefly used as the acetate, owing to its sharp, fruity, banana-like odor, is liable to disagree with many stomachs. The benzoate was administered either in the form of an alcoholic solution or, dissolved in oil, in the form of capsules. Occasionally, intramuscular injections were also employed, in which case both the benzyl-benzoate and the benzyl-acetate were given in oil.

The clinical conditions in which the benzyl esters were given and their administration was followed by remarkable pharmacologic and therapeutic results can be summarized as follows:

1. Excessive peristalsis of the intestines, such as in diarrhea and dysentery. Here truly remarkable results were obtained. Diarrheas of long standing, both in young and old persons, were quickly checked by a brief employment of benzyl-benzoate by mouth; and even cases of dysentery were also greatly benefited by it.

2. Intestinal colic and enterospasm, both of a postoperative and other character.

3. Pylorospasm, whether of functional character or produced

reflexly by ulcers and neoplasms. In these cases the effects of the drug could be and were studied by the roentgen-ray method.

4. Spastic constipation, in which there was a tonic spastic condition of the gut. This was relaxed by the antispasmodic action of the benzyl radicle and relieved the condition.

5. Biliary colic: A number of cases of gall-stone colic were treated very successfully with benzyl-benzoate.

6. Ureteral or renal colic: The author has collected a number of such cases treated with the benzyl esters, with very good results.

7. Vesical spasm of the urinary bladder. Here also a number of cases were treated, with very remarkable results.

8. Spasmodic pains originating from the contractions of the seminal vesicles. At least two cases have been found with such pains, in both of which great relief was experienced after the administration of benzyl-benzoate.

9. Uterine colic: The author has a record of a large number of cases of spasmodic dysmenorrhea in which complete relief was obtained after one or two doses of benzyl-benzoate by mouth.

10. Arterial spasm: Under this heading the author includes a large number of cases of hypertension or high blood-pressure. It was found that the administration of benzyl-benzoate by mouth markedly lowered the blood-pressure, both systolic and diastolic, in practically all such cases, the effect being more lasting than that produced by the administration of nitrites. Indeed, cases which did not respond to the nitrite treatment often responded with a falling blood-pressure after administration of benzyl-benzoate. The author has been giving benzyl-benzoate by mouth to a large number of nephritics over long periods of time. No deleterious effects on the kidney function have been noted in any of these; the hypertension, however, has been greatly improved in most of them. The effect of the benzyl treatment on the arterial wall is seen from the fact that in cases of high blood-pressure benzyl treatment produces a fall not only in the systolic but also in the *diastolic* readings. Thus, in one case after administration of benzyl-benzoate by mouth the blood-pressure fell from $\frac{200}{140}$ to $\frac{180}{115}$; in another case from $\frac{320}{160}$ to $\frac{255}{140}$; in another case from $\frac{194}{100}$ to $\frac{178}{80}$; in another case from $\frac{215}{145}$ to $\frac{190}{135}$.

11. Cases of bronchial spasm: It was found that benzyl-benzoate

was capable also of producing relaxation of the bronchial spasm in patients suffering from true asthma. Inasmuch as the term asthma is applied to a large variety of conditions, and even bronchial asthma is etiologically not a single entity but produced by a great many factors, it was natural to find that not all cases of asthma responded to the treatment. It may be stated, however, that wherever there were signs of bronchial constriction or spasm, benzyl therapy produced relief in almost every case. The author has collected at least about 25 such cases.

While the indications for the exhibition or administration of the benzyl esters, as described above, are manifold, it will be seen that the rationale of the treatment in all the cases is fundamentally one and the same—namely, that it is due to the inhibitory and tonus-lowering or spasm-relaxing action of the benzyl grouping on smooth muscle. A complete pharmacological study of the benzyl esters, with further therapeutic observations, will be published in due time in the *Journal of Pharmacology and Experimental Therapeutics*. Sufficient clinical data, however, have already been obtained by the author to warrant the recommendation of their trial in suitable cases by other physicians. In conclusion, the author may add that it is a source of special satisfaction to know that while the pharmacological properties and therapeutic uses of the benzyl esters constitute a new discovery, the esters themselves are well-known chemicals, and therefore cannot be patented or exploited by unscrupulous parties. It is therefore hoped that their employment in therapeutics may contribute to the alleviation of suffering humanity to the fullest extent.

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ACUTE PANCREATITIS IN TYPHOID FEVER

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This case is recorded because of the rarity of the occurrence of pancreatitis in typhoid fever and on account of the difficulty of recognition through the close simulation of cholecystitis. It suggests the possibility that certain of the cases which we have regarded as cholecystitis in typhoid fever were really pancreatitis.

Summary: *Typhoid fever with normal course; in convalescence abdominal pain, jaundice, leukocytosis and acute signs in the upper right quadrant of the abdomen; profuse gastric hemorrhages and bloody stools, also hematuria; a mass in the region of the gall-bladder; operation; mass found to be the enlarged head of the pancreas; recovery.*

The patient, S. L., male, aged twenty-two years, a brass moulder, was admitted to my service in the Pennsylvania Hospital on October 8, 1917, on the eleventh day of the disease.

The *past history* showed nothing of importance. He gave no history of any previous acute disease and had not had any digestive disturbance.

The *present illness* began eleven days before admission with chilly feelings, cough, some pain in the chest and difficulty in breathing. There was no abdominal pain. He complained somewhat of headache and noticed that his hearing was not as good as usual.

Examination showed a very toxic patient with slight dyspnea but no cyanosis. The lips and tongue were dry and the tongue heavily coated. Rales were heard on both sides of the chest. The abdomen was somewhat distended, showed typical rose spots and the spleen was readily felt. There was complaint of a certain amount of general abdominal tenderness, but a thorough examination was

readily made and there was no mass felt. The blood count showed 7000 leukocytes and a blood culture did not give any growth. The course was typical of typhoid fever except that the temperature curve showed a great deal of variation, at times from normal to 104° within twenty-four hours. A well-marked positive agglutination reaction was given. The temperature reached normal on October 21, the twenty-fourth day of the disease.

On October 23, the twenty-sixth day of the disease, the patient complained of abdominal pain which he referred to the upper right quadrant. On examination slight jaundice was noted which had not been present before. On palpation there was distinctly more resistance on the right side of the abdomen with definite tenderness opposite the navel and a little outside the right nipple line. There was no tenderness in the right iliac fossa. The leukocytes were 11,700 per cmm. The pain continued, the jaundice increased somewhat, and on the next day there was distinct tenderness over the upper right quadrant of the abdomen. There was definite resistance on palpation over the upper right rectus and there seemed to be a mass felt underneath. The signs were quite acute on October 26 and the leukocytes had risen to 20,300 per cmm. After the pain had persisted for about five days it lessened and for some days the patient was quite comfortable. The leukocytes fell gradually to 10,000 on November 3. There was now a definite mass in the region of the gall-bladder which was tender on more than the slightest palpation. On November 4, the thirty-eighth day of the disease, the pain returned with greater severity, and there was marked resistance in the upper right abdomen. He vomited large amounts of blood on four occasions and following this had four bloody stools. The leukocytes rose to 26,000. On this day the blood coagulation time was four minutes. On November 9, the patient looked very badly, probably due to the loss of blood, and cried frequently with pain. Abdominal palpation was unsatisfactory on account of the rigidity on the right side. On this day he again vomited a large amount of blood and passed blood in the stools. At this time for two days red blood cells were found in the urine. On November 10, the patient felt better and there was less abdominal rigidity, so that it was possible to *see* and *feel* a distinct mass in the

region of the gall-bladder. Two days later the abdomen was almost scaphoid and a distinct mass was felt in the upper right abdomen which we regarded as an enlarged gall-bladder. It was somewhat tender but not extremely so. Following this the pain again increased and the patient began to vomit, the vomitus usually containing bile but no blood. My surgical colleague, Dr. F. T. Stewart, had seen the patient several times with me and each time we discussed the question of operation. We delayed in the hope that the process might subside, but in view of the continuance of the local symptoms, the return of severe pain and the frequent vomiting, it seemed wise to advise operation. The last leukocyte count was 24,000 per cmm. One point of importance was the slight elevation of temperature; it did not go over 99° even when the acute abdominal symptoms were very marked and there was a high leukocytosis.

Operation. This was done on November 20, by Dr. Stewart. The gall-bladder and bile ducts were found perfectly normal, as also the stomach and duodenum. There was no sign of ulcer. The pancreas was found to be greatly enlarged, the head of the pancreas representing the mass which we felt through the abdominal wall. There was no evidence of any hemorrhagic pancreatitis or fat necrosis. The wound was closed, the patient did very well and made a complete recovery. On December 18, his general condition was excellent, there was no sign of jaundice and there was no visible prominence to be seen in the abdomen. On palpation there was slightly more resistance over the upper right rectus, but no mass was to be felt. The edge of the liver and the gall-bladder were not felt. Studies of the stools did not show any evidence of changes due to pancreatic disease. They were normal and fat digestion was not altered.

Remarks. The study of this case brings up several problems. 1. *The simulation of cholecystitis by pancreatic disease.* The situation of the pain, the jaundice and the local tumor all suggested disease of the gall-bladder. The jaundice was probably due to pressure on the ducts by the enlarged pancreas. The pain was very severe, more so than is usually the case in cholecystitis. One point, on which we commented before operation, was the very slight fever with such acute abdominal features. It is usual to find a higher

range of temperature in acute gall-bladder infection. The question naturally arises as to how frequently this mistake has been made. As the general rule is for typhoid cholecystitis to subside without intervention it may be that there are many more cases of pancreatitis in typhoid fever than we have recognized.

2. *The Explanation of the Hemorrhages.* The patient had a number of large hemorrhages from the stomach and from the bowel. As the blood passed from the bowel was fairly red it does not seem likely that it was blood from the stomach which had passed through the intestine. On three separate occasions there was hematuria of slight extent. Naturally this raises the question of hemorrhagic typhoid fever. However, this usually comes on during the febrile period and as a rule there is bleeding from the nose and gums, but neither occurred in this case. At operation there was no evidence of an ulcer of the stomach which might have explained the hemorrhage.

3. *The Diagnosis.* One case does not offer much basis for inferences, but there are two points which may be of some value. When the abdominal pain began there was no definite tenderness just below the right costal margin. It was slightly lower but later was as high as the costal margin. The other point is the slight degree of fever despite very acute abdominal symptoms and high leukocytosis.

As regards the frequency of occurrence of pancreatitis in typhoid fever, a search of the literature has not revealed many instances. The monographs of Keen and Hare and Beardsley do not mention it. There is more attention given to it in pathological than in clinical reports. A number of writers refer to hyperemia, enlargement and induration of the pancreas found at autopsy. Hoffman (quoted by Curschman) describes the changes as follows: "In the first period of typhoid fever the gland is generally enlarged, hard, grayish red, and even more deeply red in color. On microscopic examination there will be found dilatation and overfilling of the smaller and smallest vessels, with serous infiltration of the adjacent, still-intact parenchyma. In the later stages the pancreas, which at first was enlarged, becomes discolored and presents a grayish-yellow or even a grayish-brown appearance. Toward the end of the attack the pancreas again becomes diminished in size, and upon complete recovery acquired its normal consistence and color. In the second

stage the increase in the size of the gland appears to be dependent upon enlargement, multiplication, and active division of the cells, and the discoloration upon albuminous-fatty degeneration."

There are general references, especially in articles on pancreatitis, to its occurrence with typhoid fever. Moynihan[1] has reported a case in which pancreatitis occurred with typhoid infection of the gall-bladder. This was in a boy, aged twelve years, who had, following an attack of typhoid fever, attacks of pain in the upper abdomen accompanied by nausea but rarely by vomiting. Some months later jaundice appeared which became deeper with the attacks and decreased in the intervals but never completely disappeared. There was no fever. At operation, eighteen months after the attack of typhoid fever, the head and greater part of the body of the pancreas were found much enlarged and hard. The typhoid bacillus was found in cultures from the gall-bladder which was drained. The patient made a good recovery.

[1] Lancet, 1903, i, 1586.

USE OF BENZYL ALCOHOL AS A LOCAL ANESTHETIC

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In the preceding communication[1] the interesting pharmacological and therapeutic properties of the benzyl esters, benzyl benzoate and benzyl acetate, were described. It has already been stated that when taken into the organism the benzyl esters are transformed into hippuric acid and excreted as such in the urine. Inasmuch as this transformation probably involves a transition from the esters through the alcoholic stage, the author naturally made an investigation of the pharmacological actions of benzyl alcohol. It may be briefly stated that it was found that while benzyl alcohol can also in a measure produce the benzylic effect on smooth muscle exhibited by the benzyl esters, for other reasons to be described in a future paper this drug is not suitable for therapeutic use as an antispasmodic. At the same time a new and unexpected property of benzyl alcohol was discovered in this connection. The author found, while incidentally tasting a minute quantity of this substance, that his tongue was completely anesthetized by it. On tasting the drug a slight irritation was at first experienced; this was followed quickly by a sensation of numbness, coolness and hardness, very much like the sensation experienced after tasting cocain. This interesting observation was immediately followed up by the author and experiments were undertaken to determine more accurately the action of benzyl alcohol on sensory nerve endings and on nerve conduction, on the one hand, and its toxic effects, on the other. It was soon found that this body was possessed of powerful local anesthetic properties and was but very little toxic. The complete pharmacological data on the subject as well as the toxicology of benzyl alcohol and clinical experiences with it up to date appear in the April

issue of the *Journal of Pharmacology and Experimental Therapeutics.* In this place only a brief summary of the results obtained will be given.

Physical and Chemical Properties. Benzyl alcohol or phenmethylol is a simple organic compound having the empirical formula $C_6H_5.CH_2OH$. It is found in nature in a free state in oil of jasmine and in the form of esters in balsam of Peru, balsam of tolu and storax. It is a clear liquid, colorless, with a faint aromatic odor and the specific gravity of 1.0507 at 15.9° C. Its boiling-point at ordinary atmospheric pressure is 204.7° C. A very fortunate provision of Nature is the fact found by the chemist R. Meyer[2] that benzyl alcohol is soluble in water up to 4 per cent. at 17° C. This is of great practical importance, as for clinical purposes the author has confined himself to the use of solutions of from 0.5 per cent. to 4 per cent., and in most cases to a 1 per cent. solution in physiological saline.

Pharmacological Action. 1. *Anesthetic Effect.* The local anesthetic action of benzyl alcohol can be demonstrated experimentally in various ways. In the complete pharmacological paper already referred to experiments on sensory nerve endings and nerve trunks were made in the following ways:[3]

(*a*) Action on the mucous membranes and the skin of the human being.

(*b*) Anesthetic effect on the sensory terminals of the frog's skin: This method briefly consists in suspending a frog, the brain of which has been destroyed but the spinal cord left intact, and dipping its lower limbs in a weak acid solution. The irritating effect of the acid on the sensory nerve terminals produces a reflex movement of self-defense. On immersing such a frog for one minute in a 1 per cent. solution of benzyl alcohol, complete anesthesia of the skin is produced, so that subsequent immersions in the acid solution produce no reflex response. Control experiments made with aqueous solutions of ethyl alcohol even three and four times as strong produce absolutely no anesthetic effect.

(*c*) Anesthesia of the cornea: One per cent. solution of phenmethylol instilled into the conjunctival sacs of rabbits or dogs produces complete anesthesia of the cornea in a few minutes.

(*d*) Experiments in blocking nerve fibers, both sensory and motor, by Sollman's method[4] and Dixon's[5] method showed that benzyl alcohol in concentrations of from 1 per cent. to 3 per cent. produces complete blocking of the nerves, the sensory fibers being paralyzed before the motor.

2. *Circulation.* The effect of therapeutic doses and even much larger doses of benzyl alcohol administered in the form of aqueous solutions of from 1 per cent. to 4 per cent. manifests itself almost exclusively on the bloodvessels. Here the characteristic vasodilatation and fall in blood-pressure noted after the benzyl esters is produced. The benzyl alcohol does not affect the heart itself until enormous toxic doses are administered.

3. *Respiration.* Therapeutic doses, and even much larger doses, of a 1 per cent. solution of benzyl alcohol injected intravenously into rabbits and dogs (as high as 5 to 15 c.c. per kilo weight of the animal) produce no appreciable change in the respiration. Indeed, after small doses of the drug there may be a primary stimulation of the respiratory center. On pushing the drug, however, to its toxic limit the respirations begin to fail and death of the animal after fatal doses of benzyl alcohol comes through paralysis of the respiratory center, the heart continuing to beat for five minutes or longer after the cessation of respiratory movements.

4. *Central Nervous System.* Ordinary therapeutic doses of benzyl alcohol (5 to 10 c.c. of a 1 per cent. solution per kilo) injected intravenously into rabbits and dogs are followed by a sedative effect, the animal lying quietly and seeming somewhat narcotized. Very large doses of benzyl alcohol produce deleterious effects on the central nervous system, smaller animals especially often developing convulsions, which are followed by paralysis of the respiratory center. This effect, however, is a toxic one and never produced by doses of benzyl alcohol used for local anesthetic purposes and even by much larger doses than these.

Toxicology. The effect of very large doses of benzyl alcohol on mice, rats, guinea-pigs, kittens, cats, rabbits and dogs was studied. The complete data need not be here given. We may briefly state that the minimum lethal dose of alcohol for all the animals studied is very much greater than that of all the ordinary well-

known anesthetics. Perhaps a clear idea of this low toxicity may be gained by stating that injections of 20 c.c. per kilo of a 1 per cent. solution or 5 c.c. per kilo of a 4 per cent. solution intravenously in rabbits and dogs produced no deleterious effects.

Effect on Tissues. Inasmuch as a local anesthetic, in order to be of practical utility, must not produce extensive destruction of tissue into which it is injected, observations were made on the action of benzyl alcohol in this respect. It may be stated in this place that aqueous or saline solutions of benzyl alcohol in concentrations of from 1 per cent. to 4 per cent. injected subcutaneously or intramuscularly were never found to produce any marked irritation or destruction of the tissues into which they were injected. Certainly no more irritation was produced by benzyl alcohol than by equivalent amounts of cocain and certainly, also, much more local irritation was produced by local injections of quinin-urea than by injections of benzyl alcohol solutions. The most marked irritation following the use of benzyl alcohol solutions was noted in case of the conjunctiva, in which cases considerable congestion was seen; but this vasodilatation could be easily antagonized by the additions of small quantities of epinephrin to the anesthetic.

Clinical Experiences. In view of the marked local anesthetic properties of benzyl alcohol, even in weak aqueous solutions found in the laboratory experiments, and in view of the comparatively low toxicity of the drug, as also determined by numerous experiments, and, furthermore, in view of the great difficulty in obtaining the common well-known local anesthetics on the market on account of the present war conditions, it was deemed justifiable to give benzyl alcohol very cautiously a trial in clinical cases. Accordingly, with the kind coöperation of the surgeons in charge, the author had benzyl alcohol administered as a local anesthetic in a number of surgical cases in which it was necessary to perform minor local operations under local anesthesia. Some of these cases were treated in the Out-patient Department of Professor William Halsted at the surgical clinic of the Johns Hopkins Hospital, and others were performed outside. Up to the present time the author has collected 45 such cases. In these, surgical operations of a lesser or greater extent were performed with local anesthesia produced by benzyl alcohol and

the results obtained were highly successful. A resumé of the clinical cases will be found in the author's complete paper. In this place it may be stated that operations ranged from an incision of an abscess to the complete extirpation of external and internal hemorrhoids. Two cases of ingrown toe-nail were operated upon, with complete success, under this anesthetic, the tissues being excised and scraped without the patient feeling any pain. Inasmuch as benzyl alcohol is comparatively very little toxic, a number of extensive plastic operations have also been performed by Dr. J. S. Davis while employing it as a local anesthetic. In one of these cases as much as 30 c.c. of a 1 per cent. solution was injected without any toxic effects. The author has also collected a series of dental cases in which benzyl alcohol was injected for the purpose of extraction of teeth.

Summary. 1. Laboratory experiments with benzyl alcohol or phenmethylol show that it possesses powerful local anesthetic properties, on the one hand, and a very low toxicity as compared with other well-known local anesthetics, on the other.

2. A series of clinical cases in which weak solutions of benzyl alcohol were injected for the performance of surgical operations proved also that the drug is an efficient local anesthetic in surgical cases.

3. It is considered that the anesthetic efficiency, the low toxicity, the simple excretion of the drug by the organism and the ease with which benzyl alcohol solutions can be sterilized on account of its high boiling-point will render it a useful local anesthetic in practice.

In conclusion, the author wishes to express again his satisfaction at the fact that while the anesthetic properties of benzyl alcohol constitute a new discovery, the drug itself is a well-known chemical, and therefore cannot be patented or exploited by unscrupulous individuals. It is therefore hoped that it will contribute its share to the alleviation of suffering mankind in this critical war time.

The author wishes to express his deep appreciation for the coöperation in testing the drug on clinical cases to the surgeons, Drs. R. H. Follis, O. Pancoast, J. Staige Davis, H. L. Homer and A. Hebb; and to the dentists, Drs. B. Holly Smith, Jr., and I. L. Mansbach.

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THE CLINICAL MANIFESTATIONS OF TROPICAL SPRUE[1]

By EDWARD J. WOOD, M.D.
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Before this Association, in 1915, I ventured to ask attention to the occurrence of tropical sprue in the Southern States among those who had not visited out of the States. Since that time the number of cases has increased and the disease is slowly becoming one of importance in these States.

Having nothing new to add about the nature or the remedy for the condition, it is with some reluctance that I bring the matter up again for your consideration, but having in mind the location of so many of our larger cantonments in the South, it may be useful to the medical officers who have not seen the disease to have the possibility of its occurrence brought to their attention again. This feeling is rather intensified by the fact that the disease is being overlooked in some of our largest city clinics in the North.

Sprue is being very generally confused with pellagra. In fact, there has been an effort in the past by at least one observer to show that the two diseases are one and the same. Even a very elementary knowledge of either disease would settle this point to the satisfaction of any observer. The facts are that sprue never causes an eruption on the skin, while in the case of pellagra a diagnosis without this group of symptoms is seldom if ever justified. Sprue produces a profound anemia, which is markedly absent in uncomplicated pellagra.

The feces in sprue differs markedly from the feces in pellagra.

[1] Wood, E. J.: The Occurrence of Sprue in the United States, Am. Jour. Med. Sc., 1915.

In sprue the movement is large, pultaceous, light in color, acid in reaction, passed chiefly in the early hours of the day, unattended with pain or tenesmus. In sprue there is a large fat and nitrogen loss which does not occur in pellagra.

The question of the relation of the pancreas to sprue is one of great interest and importance. In many cases of sprue there does occur a definite impairment of pancreatic function which may be determined in any of the usual ways. Again, there are typical cases of sprue in which the pancreatic function is remarkably good. Mayo Robson, many years ago, pointed out the fact that in sprue there may occur the complication of a definite pancreatitis. Much can be expected from the study of the duodenal contents in the future. Some work has been done along this line, but much more is needed.

The anemia in sprue is usually regarded as a simple anemia. In many cases the color index is as much as 1.25, but this point is seldom reached except toward the end of a fatal case. The morphological changes do not suggest pernicious anemia, though the marked tendency to remissions will always demand a careful consideration of this possibility. The hemoglobin frequently reaches 20, the patient is slightly edematous and the picture presents one of the cachexia of malignancy. It is remarkable how great an improvement may occur in such cases even when this point is reached.

Much has been said about the decrease in the size of the liver. To us this has seemed a point of small importance, especially as it may occur in so many other nutritional conditions.

The tongue in sprue is not so important as one would gather from the literature. In the Southern cases the tongue answers to the requirements of the classic description of the disease, but in such mild form that there is little complaint on the part of the patient, and it often appears remarkably normal. It is apt to be red, somewhat enlarged and denuded. In the beginning there may be found papillary enlargements, with redness. The terrific salivation of pellagra does not occur. The very painful and extensive ulceration in pellagra, likewise, is absent. There does occur in some cases of sprue ulcers on the tongue opposite the last teeth known as Crombie's molar ulcer, but both in extent and painfulness is not comparable to the distressing condition so familiar to any observer who has seen

many cases of pellagra. In pellagra the tongue is of a much deeper red color, it is markedly pointed, while in sprue it is large and rather flabby. Swallowing in pellagra often causes extreme pain, which seldom is the case with sprue.

Our cases of sprue have come from the Philippines, Porto Rica and the Southern States. There can be no doubt that the disease is the same in every locality. It may vary in intensity, but usually on investigation it will be found that it is more a question of the length of duration of the case than the geographical origin.

Probably the first thing which attracts our attention to the possibility of sprue is the tremendous amount of feces passed in a single day. In a Porto Rican case I was told that the patient filled half-full a large bed-room slop-jar in a single day. This characteristic was pointed out by the late J. H. Musser as being distinctive of pancreatic insufficiency, and even in sprue this is often the case. The patient will begin getting up at 4 A.M., and having what they describe as a "scouring-out" movement, at short intervals, until about noon, when there is usually a cessation until the next morning, when the program is repeated.

Sprue is a very chronic disease, subject to marked remissions. It appears that remissions will occur spontaneously, with or without treatment. No drug in my hands has accomplished anything. The beef diet of J. Cantlie, together with absolute rest in bed, well protected from cold by blankets and the free drinking of hot water, will accomplish most. The beef is finely chopped and cooked very lightly. It is given in four-ounce portions four times in the twenty-four hours. Three pints at least of hot water must be taken in the same period. It is remarkable to note the rapid improvement in the anemia under this treatment. After improvement is well established, toasted bread crumbs are added. If the patient is very ill it may be necessary to give the expressed juice of the fresh beef in teaspoonful portions at short intervals. Owing to the invariable decrease or total absence of hydrochloric acid in the stomach contents, it might be well to add this drug to the treatment. But without hydrochloric acid the disease improves rapidly under the meat diet.

FURTHER OBSERVATIONS ON THE BACTERIA OF THE INTESTINAL TRACT

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At the last meeting of the Association attention was called to the great increase of large Gram-positive bacteria in the dejecta in certain feeding cases in children and to the results of the study upon the isolation and identification of these organisms. During the progress of this investigation we came to the conclusion that these bacteria were chiefly the aërobic spore-bearers identical with the species common to the environment, to air, dust, soil, milk, water and food, and that they were not anaërobic bacteria, as is usually believed. The opinion was further hazarded that the presence of these organisms was in some way associated with their presence in the food upon which the children were being nourished and could not be regarded as of any clinical significance in the light of the present conflicting evidence. In continuing these investigations two main lines of inquiry naturally presented themselves: On the one hand there was the important question as to the significance of these organisms and the further inquiry as to whether they, as well as other species not ordinarily regarded as normal to the intestines, are increased as a result of the introduction of certain foodstuffs into the diet. Studies upon this question have now been started upon rats in connection with Dr. MacCollum, but the problem is so complicated as not thus far to have yielded results worthy of note. On the other hand there is the question as to whether this interpretation of the previous findings is correct and as to whether these Gram-positive organisms may not sometimes be anaërobes. This last problem has been undertaken the past year at the Rocke-

feller Institute for the Study of Animal Diseases at Princeton, through the courtesy of Dr. Theobald Smith, and it is the results of this study with some subsequent work in Baltimore which we wish to report today.

In the course of the work at Princeton an examination was undertaken of the stomach and various portions of the intestinal tract in eleven young calves, several of them apparently normal and several of them suffering from mild intestinal derangements resembling the beginning stages of the condition known as "scours." In all these animals a careful study was made of the bacteria found in smears from the contents of the alimentary canal and from the wall of the mucosa and correlation attempted between the species found in the cultures and the forms observed in the smears. As a result of this work it is clear that the previous opinion as to these Gram-positive organisms is essentially correct. In all of the animals examined large Gram-positive bacteria were represented in every part of the gastro-intestinal canal. The cultures from the same areas revealed species which had the same morphology and staining reactions. In general the organisms isolated in Princeton were the same as those obtained in Baltimore, except for minor variations, and their presence was so constant as to make it appear that Gram-positive spore-bearing bacteria are almost as much normal to the intestines as are the so-called obligate bacteria of that tract and merely require special efforts for their isolation. Manifestly, however, the question of the identification of the Gram-positive bacteria seen in smears from the contents of the bowel cannot be answered positively without at the same time considering the anaërobic bacteria which may be present there. Therefore, in six of these animals anaërobic cultures were taken from the same parts of the alimentary canal as were employed for the aërobic. With the present methods of studying anaërobes this inquiry is necessarily limited to the study of spore material. In four of these cases the anaërobic cultures on blood-agar were negative, and the opinion was thus reinforced that the large Gram-positive elements which had been observed were chiefly aërobes. In two cases the anaërobic plates gave cultivations of large Gram-positive bacteria, which are of special interest at the present time. One of these cases proved to

have an unidentified anaërobe mixed with the "gas bacillus." A study of the smears revealed no Gram-positive organisms with the morphology of these two anaërobes, so that the cultures must have represented spore material. These species were therefore probably not vegetating in the intestinal contents. This could not, however, be regarded as final, since there are certain differences between the morphology of organisms when found in the intestinal juices and when cultivated on artificial media even when they are manifestly the same species. It was therefore necessary to resort to other methods, such as the demonstration of encapsulated bacteria in the intestinal smears. In the absence of any method of cultivating the intestinal anaërobes in the presence of intestinal aërobes, it was felt that positive cultures of the "gas bacillus" from spore material and positive findings of encapsulated organisms in the intestine with the morphology of the "gas bacillus" were the best evidence which could be secured as to the actual multiplication of this organism in the animal body. Heretofore all search for encapsulated bacteria in the dejecta has been negative in our hands and no satisfactory method of demonstrating bacterial capsules in the intestinal contents was available. In May of last year, however, Dr. Huntoon, of New York, published the details of a new method of staining capsules by the use of nutrose and lactic acid as a fixative and carbol fuchsin as the dye. The ease of application of this stain, its reliability and its availability for the study of mixtures of bacteria, such as one finds in the succus entericus, make this one of the most valuable contributions to bacteriological technic of the past few years. It is now possible to determine whether the bacteria in the intestines are encapsulated or not. In the first case above mentioned the absence of demonstrable encapsulated bacteria in the smears makes it reasonably certain that the anaërobic cultures represented only spore material and that the "gas bacillus" was not actually vegetating in the intestine. The other case was of exceptional interest. Here the smears from the upper part of the gastro-intestinal tract above the ileocecal valve showed an abundance of large Gram-positive bacteria but no encapsulated forms. The aërobic plates were full of the ordinary spore-bearers similar to the species which had been previously isolated. The anaërobic plates

were sterile. Below the ileocecal valve the smears from the intestine were also full of Gram-positive organisms. When the smears were stained by Huntoon's method practically all the large bacteria proved to be encapsulated and to have the morphology of the Welch bacillus. The aërobic cultures from this region were devoid of Gram-positive organisms while the anaërobic cultures were full of typical "gas bacilli." There is then this condition, an abundance of Gram-positive bacteria above the ileocecal valve and positive findings of aërobic organisms and no anaërobes, with an abundance of encapsulated bacteria below the valve with no Gram-positive aërobes but many Gram-positive anaërobes. We must therefore modify the original conclusion and say that while in the majority of instances the Gram-positive elements in the intestines are represented by Gram-positive aërobes in cultures, in exceptional cases one anaërobe at least, Bacterium Welchii, finds conditions for its vegetation in the intestine, possibly only in the large gut. The importance of this finding relates not to this particular case but to its general application. This is possibly the first instance in which evidence is satisfactory that the "gas bacillus" is actually multiplying in the intestine, although a number of authors have regarded this possibility as of distinct importance in relation to certain clinical conditions. It is evident that this observation opens up again the question as to whether the multiplication of this species in the intestinal tract can in any way be associated with diseased conditions in man.

Let us now turn for a moment to the consideration of some related observations which have been conducted in Baltimore. Several years ago, in association with Dr. Pryor, of the United States Navy, it was demonstrated that practically all samples of Baltimore milk pasteurized in the laboratory by heating to temperatures from 65° to 80° C. for fifteen to thirty minutes decompose with a violent explosive reaction. This procedure destroys all the vegetative bacteria in the milk and accomplishes what we aim to accomplish by commercial pasteurization. This reaction is due to the development of the "gas bacillus," which is always present in spore form in Baltimore milk. Subsequently, in association with Dr. Lawrence, we were able to study the properties of commercially pasteurized

milk allowed to decompose, this change being due to the "gas bacillus" and of milk cultures of this organism. The neutralized whey from both sources contained hemolytic substances which represent a true bacterial hemolysin developed by the bacillus of Welch and Nuttall. It has always been known that the filtrates in addition to the possession of hemolytic properties were toxic to small animals, and during the past year the work upon these cultures has been continued. Milk cultures of the "gas bacillus," after filtration from the grosser particles of curd and after the intense acidity is neutralized by caustic potash, are poisonous to both rabbits and guinea-pigs by subcutaneous inoculation. The reaction is quite characteristic. The animals die in from twenty-four to forty-eight hours, with an intense necrosis of the tissues of the abdominal wall, with an abundant gelatinous exudate stained with hemoglobin and with large gas blebs in the axillary and inguinal areas. Smears from various regions show nothing but the "gas bacillus," and pure cultures of the organism may be obtained by ordinary anaërobic methods. The toxicity of the milk culture is at its maximum after twenty-four hours' incubation, but is never very great. Guinea-pigs of 300 grams' weight practically always succumb to doses of 0.5 to 1 c.c. and rabbits of 1000 grams' weight to about 3 c.c. If the whey be filtered through a Berkefeld candle the germ-free material obtained is also poisonous and hemolytic. In both guinea-pigs and rabbits it produces an acute intoxication, the animals dying in twenty-four to forty-eight hours and showing necrosis and gelatinous edema at the site of inoculation, this exudate being stained with hemoglobin. Rarely the animals recover from the acute effects and death occurs after the lapse of ten to twelve days. The toxicity of the material is not extreme. It has always required at least 1 c.c. of the neutralized whey to kill a 300 gram guinea-pig and usually larger quantities, 3 to 5 c.c. The poisonous qualities are apparently destroyed by heating to between 60° and 70° C. There is evidently present in this whey a true excretory product of the "gas bacillus" characterized by a low degree of toxicity, by thermolability and by fairly definite effects upon animals. Such a substance in the present state of investigation would be ranked as a bacterial poison of low potency. It possibly corresponds to the toxin found by Bull in his

tissue-fermentation cultures of the "gas bacillus," except that Bull's cultures are much more toxic than anything thus far obtained from milk. Studies upon the poisonous properties of old pasteurized milk and of milk cultures of the "gas bacillus" are being continued in the hope of clearing up some of the doubtful points. For the present we desire only to point out that milk cultures of the "gas bacillus" are always poisonous to animals both before and after filtration, and that we are now in a position to determine if this organism is capable of vegetating in the intestinal tract in selected cases. It remains to be seen whether these two findings have any etiological significance in relation to the cases of scurvy which it has been claimed may be brought about by the prolonged use of pasteurized milk.

MOISTURE IN THE AIR SPACES OF THE LUNGS AND OXYGEN THERAPY

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While on duty at a casualty clearing station in Flanders in the summer of 1917, the writer observed several respiratory phenomena associated with foam in the air passages which conferred an entirely new significance on the presence of moisture in the bronchial tree.

The patients who exhibited these symptoms were men who inhaled phosgene and chlorine.

These patients had, essentially, a large amount of plasma poured out into the air spaces of the lungs which was not secondary to incompetence of the left ventricle. It was a severe primary edema of the lungs unassociated with myocardial incompetence.

One of the things that impressed the observer was the disproportion between cyanosis and air hunger. The evidence of cyanosis was very much more pronounced than was air hunger in most of the patients.

Another very striking experience was the manner in which patients were relieved of cyanosis by the inhalation of oxygen, and the fact that the relief of cyanosis was not attended with any change in the volume or rate of respiration; and subjectively the patients were not made more comfortable from the inhalation of oxygen.

If a gassed patient whose bronchial tract is filled with foam and has cyanosis breathes pure oxygen, he is relieved of cyanosis, but the relief does not come promptly. It is unlike relief from cyanosis which has been caused by laryngeal obstruction. When a patient suffering from cyanosis due to laryngeal obstruction has

the obstruction relieved, cyanosis disappears within a few seconds and the patient is instantly made comfortable. The gassed patient was not relieved of cyanosis until after he breathed pure oxygen from three to five minutes. The patients could not tell when they were breathing oxygen and when they were breathing atmospheric air. In fact, they preferred to be relieved of having a mask over their faces, although this method gave them the greatest relief from anoxemia. Evidently the psychic affect of the obstructing mask contributed to their discomfort, and they begged to be relieved of it. They preferred to have the stream of oxygen conducted into their respiratory tract by way of a soft rubber tube inserted in the nostril, although by this method I did not see a single case in which cyanosis was diminished. It is quite apparent that cyanosis and air hunger did not develop apace with each other and that anoxemia could be relieved without giving any relief to air hunger. The problem which requires an explanation is, how anoxemia and air hunger are largely dissociated when breathing atmospheric air, and why is only cyanosis favorably affected when the patient breathes pure oxygen?

It has been suggested that the dissociation is due to the film of moisture which intervenes between the ventilating air and respiratory membrane. Carbon dioxide is twenty-five times as soluble in water as oxygen, and consequently the escape of carbon dioxide from the blood is much better fulfilled than the absorption of oxygen. Carbon dioxide can escape from the blood, but oxygen is absorbed in much smaller amounts. This explanation obviously will not satisfy the clinical experience. If according to the predicate on which this theory is advanced, the patient is suffering from anoxemia and has an adequate escape from carbon dioxide acidosis, then the abrogation of anoxemia should give the patient perfect comfort. There is another point about this theory which is not consistent with the facts. Plasma in the bronchial tree and respiratory units does not lie as a film of moisture but occupies the air space as foam. At the end of an expiration the entire air space of the lung from the nares to the respiratory membrane is occupied by foam. The total volume of this foam must amount to at least 1200 c.c., and during inspiration all of the contained

foam is aspirated into the air spaces and will be unequally distributed throughout the respiratory units. Some units will be filled with foam, and no doubt many units will contain no foam whatever. This foam is alveolar air foam, and when it has acquired the same partial pressure of CO_2 as the affluent blood to the lung, all escape of CO_2 from the blood into the unit occupied by foam will be impossible. When a respiratory unit is full of alveolar air foam the only area for escape of CO_2 will be the cross-section of bronchi which supply any portion of the lungs thus affected.

The fact that the circulating blood in the lung of a normal person at rest is able to contribute 20 c.c. of CO_2 to the ventilating air during each respiratory cycle is due to the large area of the respiratory membrane.

The following experiment illustrates the significance of the area of the cross-section of a communicating path between two fields of different partial pressures of a gas:

Two 3-liter bottles were furnished with a connecting tube which was 20 cm. long and had a diameter of 1.5 cm. One bottle contained 19.5 per cent. of CO_2 and the other bottle contained 0.1 per cent. CO_2, both at barometric pressure. The communication between the two bottles was established and specimens of air were taken from each bottle by employing a device which enabled us to remove specimens of air from each bottle without disturbing the barometric pressure.

The following results gives the comparative concentration of CO_2 in each bottle at a given time.

Time.	Per cent. CO_2 in A.	Per cent. CO_2 in B.
11.35	0.1	19.5
11.45	1.25	18.2
11.55	3.25	17.0
12.55	3.75	15.3
1.25	4.85	13.9
2.40	6.20	11.4

The same experiment was then repeated by using a connecting passage of the same length as in the first experiment, but with a lumen of 5 cm. The following results were obtained:

Time.	Per cent. CO_2 in A.	Per cent. CO_2 in B.
11.30	13.7	1.2
11.40	7.3	7.0
12.00	6.4	6.4
12.20	6.4	6.3

This simple experiment is given merely to cite the fallacy in thinking of partial pressure as synonymous with barometric pressure. It also enables one to visualize the significance of communicating area in establishing equilibrium of partial pressure between two gas fields of different concentrations.

If a respiratory unit is filled with alveolar air foam, then the area for the evolution of CO_2 is manifestly cut down from the large area of the respiratory membrane to the cross-section of its bronchiole, and if at the end of an expiration the entire air space of the lung is filled with foam, the only area for the escape of CO_2 is the cross-section of the trachea. It seems perfectly clear that any portion of the respiratory membrane which is covered by alveolar air foam will be deprived of its normal respiratory function, both for the escape of carbon dioxide and the absorption of oxygen. If at the end of a deep inspiration there is an unequal distribution of foam throughout the air spaces, different portions of the pulmonary blood will be ventilated in different degrees. If the patient takes a deep inspiration of 2000 c.c. he will then have superventilation of some of the air spaces, and, consequently, superventilation of the blood in these respiratory units; but the air spaces occupied by foam will be eliminated from the respiratory function. Consequently, we will have admixtures of varying degrees of venous and arterial blood going to the left auricle. From the superventilated unit there will be contributed an effluent blood with saturated oxyhemoglobin and a partial pressure of CO_2 less than normal. From the foam units there will be contributed a blood with a high CO_2 content and a low oxygen content. The total effluent blood from the lung under such circumstances will then contain an increase of CO_2 partial pressure and a low oxygen content. The superventilated units compensate in some measure for the want of ventilation in the foam units so far as the partial pressure of CO_2 is concerned, but they cannot compensate for anoxemic blood which comes from the foam units, and this I conceive to be the source of the disparity between anoxemia and air hunger in gas poisoning.

Now what will happen if the patient breathes pure oxygen? When pure oxygen is breathed it will require several minutes

before the alveolar air foam will have been changed to oxygen foam, and when the oxygen foam is once formed, what will have been accomplished for respiration? The foam units will have their entire respiratory membrane exposed to oxygen foam, and thus the area for the absorption of oxygen will have been many times increased. What has been accomplished for the ebullition of carbon dioxide? That will remain the same as when the patient is breathing atmospheric air and leaves the CO_2 content of effluent blood of the lung unchanged; but anoxemia will have been disposed of. This I conceive to be the explanation for the clinical fact, that after the inhalation of pure oxygen for a period of three to five minutes the patient regains a normal color but retains the same respiratory discomfort. This idea of the admixture of unrespired blood in the effluent stream has been ignored in clinical practice, yet we have an abundance of evidence that it occurs in congenital heart disease, occlusion of a single bronchus, lung consolidations and moisture in the bronchial tree.

A child with open interventricular septum and open ductus Botalli will be cyanotic, but has no air hunger when at rest. If he is given pure oxygen to breathe the cyanosis remains unchanged, for under such circumstances the unrespired blood does not come in contact with the respiratory membrane. If the child exercises, cyanosis will rapidly increase and so will partial pressure of CO_2 in the aortic blood rapidly increase. Consequently, with exercise, cyanosis and air hunger increase in equal paces with each other.

If such a patient is instructed, while quietly sitting, to employ forced breathing for three minutes, cyanosis will diminish. But under these circumstances, ventilation of the lung and oxygenation of the blood and minute volume flow of blood through the lung will all be greatly increased. Thus when (in *morbus caeruleus*) ventilation is increased disproportionately to the increase in gaseous metabolism, anoxemia lessens and CO_2 partial pressure in the blood will have been greatly diminished. In *morbus caeruleus* we have an admixture of superventilated blood (in which there is a low partial pressure of CO_2 and a normal oxygen content) with another stream of blood which has a high CO_2 and a subnormal

oxygen content. Consequently, there will be a disproportion between cyanosis and air hunger.

It is perfectly clear that in any disease in which unrespired blood is contributed to the aortic stream the partial pressures of CO_2 and oxygen of the alveolar air cannot be accepted as measures of the partial pressure of carbon dioxide and oxygen in the aortic blood. Gas analyses of alveolar air are applicable to the circulating blood only when every portion of the respiratory membrane exposed to ventilating air has also a normal exposure to circulating blood, and, furthermore, every part of the lung from which blood is contributed to the aortic stream there must also be a normal exposure of the respiratory membrane to ventilating air. If these two conditions are not fulfilled then interpretations from gas analyses of respired air will be erroneous.

In lobar pneumonia there is always a certain amount of cyanosis; it is a common thing to see a patient with lobar pneumonia who has pronounced cyanosis, and although the patient has moderate hyperpnea, he will deny any sensation of air hunger when he is questioned on the point. If blood flow through the pulmonary vessels of the consolidated lung is maintained, then the effluent blood from the consolidated lung must be venous blood. The superventilation of the uninvolved portion of the lung will compensate for the increased CO_2 contributed to the aortic stream from the consolidated lobe, but superventilation of the uninvolved parts of the lung will not compensate for the anoxemia which is contributed from the hepatized lung. In this mechanism we see an explanation for cyanosis without air hunger in lobar pneumonia. The cyanosis is due to anoxemia and not to methemoglobin, for when the shed blood is exposed to atmospheric air it immediately takes on the normal color of shed blood. The anoxemia is not in any way associated with the infection. It is due purely to the admixture of unventilated blood to the aortic stream. When pneumonia terminates in crisis, cyanosis persists, and finally disappears just as the exudate is absorbed and ventilation of the affected lung is resumed.

The alveolar air of a pneumonia patient cannot be taken as an expression of the gaseous content of the aortic blood. One need

only to estimate the carbon dioxide and oxygen content of the alveolar air of a pneumonia patient to be convinced of the fallacy. The patient will be cyanotic, but in spite of this the partial pressure of oxygen in the alveolar air will be higher than in a normal person and the CO_2 partial pressure will be lower than normal.

During the past winter I have had many opportunities to test out lobar pneumonia. They all have cyanosis and the cyanosis is proportionate to the area of the lung which is involved, and is not at all associated with cardiac incompetence.

For instance, if one lung is hepatized and the other lung contains no moisture, the patient will have pronounced cyanosis with superventilation, but he will not admit that he has air hunger. If such a patient is given pure oxygen to breathe, cyanosis is unaffected. But suppose the patient may have one lobe hepatized and an abundance of moisture in the remaining portions of the lung, then the inhalation of pure oxygen will partly diminish the cyanosis, but the experience of air hunger is unmodified. I think this accounts for the different views on the subject of oxygen therapy in pneumonia. A patient who is cyanotic from both lung consolidation and moisture in the air spaces will benefit from the inhalation of oxygen so far as anoxemia derived from the edematous lung is concerned, but he will not benefit from anoxemia so far as the consolidated lung is concerned.

A further proof of the origin of cyanosis in pneumonia lies in the fact that occasionally we see a patient in whom cyanosis is very pronounced and then ceases without change in the exudate. Thus two patients whom I have in mind—one seen by Dr. R. G. Pearce and one seen by myself—are patients who had one entire lung consolidated, with normal hearts and normal blood flow, so far as could be determined by physical examination, and no signs of moisture in uninvolved portions of the lungs, and then within twenty-four hours cyanosis ceased, although there was not the slightest evidence of improvement in the infection or improvement in consolidation of the lung. The only explanation I have for such a phenomenon is that during the course of the pneumonia the blood flow through the pulmonary vessels of the consolidated lung was greatly diminished at the time when cyanosis ceased.

The patient seen by Dr. Pearce died on the following day after cyanosis disappeared, and the other patient under my observation, at Lakeside Hospital, made a good recovery.

There has been thus far no direct evidence presented on which we can estimate the blood flow through the pulmonary vessels of a hepatized lung. It seems very reasonable to believe the blood flow through a hepatized lung is diminished by the loss of respiratory extension and retraction even when the pulmonary veins and arteries are patent. The anoxemia of lobar pneumonia and the fact that this anoxemia is uninfluenced by breathing pure oxygen is very satisfactory evidence of unrespired blood flow through the consolidated lung being the source of anoxemia. And the fact that anoxemia may cease or grow less during a period when fever, hepatization and cardiac output are unchanged, seems to be converse proof of the correctness of the theory.

It is a common experience to find patients with pleurisy with effusion sufficiently large to completely eliminate the lung of the affected side from respiratory function, and yet the patient may not have the slightest trace of cyanosis. In the compressed lung there is not only a want of ventilation, but there is also a great diminution in the minute volume of blood going through the pulmonary circulation of the compressed lungs. Consequently there is little or no unrespired blood contributed to the aortic stream. This view will explain the want of cyanosis in many chronic tuberculous diseases of the lung, and will also explain the presence of cyanosis in acute miliary tuberculosis.

In the chronic tuberculous lung the ischemic process and infiltration progress go hand in hand, and consequently as a portion of the lung is eliminated from the respiratory function its pulmonary circulation is encroached upon; therefore such an involved portion of the lung will not contribute unrespired blood to the aortic stream. But acute miliary tuberculosis is accompanied by an abundance of moisture in the air spaces which will contribute unrespired blood to the aortic stream.

In former years we conceived air hunger and cyanosis accompanying incompetence of the left heart to depend upon the diminished minute volume of blood passing through the lung, but since

the role of moisture in the air spaces has assumed a more important role in our estimates of air hunger and cyanosis, I have had the opportunity of testing out two cases of cardiac incompetence associated with pulmonary edema. One was a patient who had chronic cardiovascular and renal disease, with great dilatation of the heart, dilatation of the jugular veins, and a large and sensitive liver and general anasarca. The patient had intense air hunger and was coughing up great quantities of bloody foam. He was given pure oxygen to breathe by means of a mask connected with a rebreathing device, so that he breathed pure oxygen through a bag of oxygen which was inserted into the circuit and the carbon dioxide was removed from the expired air by a canister of soda lime which was introduced into the circuit.

Breathing through this closed system for about three minutes was sufficient to change the patient's color from pronounced cyanosis to a normal pink color, but the patient experienced the same air hunger and the volume and rate of respiration were unmodified.

Another patient was brought into Lakeside Hospital suffering from a head injury. The patient was in coma. He had a dilated heart and a great abundance of foam in his bronchial tree. This patient was made to breathe pure oxygen through a closed system and the same thing happened as in the patient above described. The pulmonary edema and the volume and rate of respiration were all unmodified. But after inhaling pure oxygen for about three minutes the patient regained a perfectly normal color and retained the normal color for a period of about four hours, during which time he breathed pure oxygen through the closed system. At the end of that time the patient died from cardiac failure, and although he had cardiac dilatation and a filiform pulse and extreme pulmonary edema, he had no cyanosis when he breathed pure oxygen.

We have here exactly the same mechanism as was cited above in cases of gas poisoning. The alveolar air foam was changed to oxygen foam. This compensates for the anoxemia which existed when atmospheric air was breathed, but it did not compensate for the increase in the partial pressure of CO_2 in the aortic blood.

Another experience illustrates the diagnostic service of this point of view in a young man, aged nineteen years, who was known

to have stenosis and insufficiency of the aortic valve, with hypertrophy and dilatation of the left ventricle. Four days before entering Lakeside Hospital he had an initial chill followed by fever. Cough and bloody sputum developed on the following day. Coarse and fine moist rales were heard over all of both lung areas. On the day previous to his admission to the hospital very severe cyanosis developed, so the attending physician and family were alarmed. The patient was deeply cyanotic, but he did not suffer from air hunger. Hyperpnea, however, was pronounced.

Chest examination revealed an abundance of moisture throughout all the air spaces of both lungs, but there was nowhere marked dulness nor any areas of bronchial breathing. The right auricle was not dilated. The cardiac signs revealed a marked enlargement of the left ventricle and moderate enlargement of the right ventricle, with auscultatory and pulse indications of stenosis and insufficiency of the aortic valve.

The sputum proved on microscopic examination to consist of blood and plasma. The number of white cells had about the same proportion to red cells as found in normal blood. The sputum in fact consisted of transudated plasma, with a large admixture of red cells.

The patient breathed pure oxygen through a closed system for rebreathing, and after about three minutes all cyanosis disappeared without any change in the rate or amplitude of respiration. The fluoroscope was then used and this showed no area of infiltration in either lung and confirmed the dimensions of the several heart chambers as determined previously by percussion and palpation.

Three days after admission to the hospital the temperature was normal, the rales and cyanosis disappeared and the patient's heart and pulse continued to show the same physical signs as on admission. This case was regarded as an instance of the disease described by Woillez. Had there been any hepatization of the lung, anoxemia would not have completely ceased with breathing pure oxygen.

Moisture may play an important part in the development of cyanosis in patients who have bronchitis, emphysema and bronchiolar spasm.

In the past we have underestimated the role of moisture in the production of anoxemia.

A young man who had bronchitis with an abundance of moisture in his air spaces had pronounced cyanosis of the lips and fingers. There was only a moderate hyperpnea. It did not amount to air hunger. There were no demonstrable areas of consolidation in the lung. The volume of the lung was very little increased, not enough, indeed, so that the pleural sinuses were filled with the lung. The patient's heart and vascular system showed no evidences of any circulatory impairment.

He breathed oxygen through the closed system, and after inhaling oxygen for about three minutes all traces of cyanosis disappeared, but the patient breathed with exactly the same rate and volume as when he was breathing atmospheric air, and he could not detect any difference in his subjective experience when he was breathing oxygen from when he was breathing air. This I conceive to be very important in estimating the functional disability in patients suffering from cardiorespiratory disease.

I am sure that in the past we have ignored the role of moisture in the air spaces and we have quite ignored the contribution of unrespired blood to the aortic stream, nor has there been any attempt to point out the mechanism of this contribution in diseases of the heart and diseases of the lung.

If, for instance, a patient with bronchitis and emphysema has cyanosis and it can be demonstrated by inhalation of pure oxygen that the patient's anoxemia has its origin in moisture in the air spaces, then the indication for a change to a dry climate is perfectly clear. If his cyanosis is unmodified by inhalation of pure oxygen, then I think it is quite clear that the presence of moisture in the air spaces does not contribute to cyanosis and a dry climate will not improve his cyanosis.

The very simplest way in which unrespired blood can be caused to flow into the aortic stream is to stop a bronchus.

About two years ago Dr. Pearce and I made a very simple experiment on a dog. A tampon of lambs' wool with string attached was pushed down through a tracheal opening into the bronchus leading to the right lobe of the lung. This, of course,

eliminated the right lobe from air ventilation but did not arrest the flow of blood through the pulmonary vessels. So far as the appearance of the buccal mucosa and tongue of the animal were concerned we could see no change in color. But during the time the tampon was in the right bronchus, blood was drawn from the femoral artery and put in test-tubes under aniline oil, so that the blood was not exposed to air. It was very apparent during the period when the bronchus was blocked the blood had a much darker color than when the bronchus was free. This was done repeatedly by withdrawing the tampon and replacing it, but at each time when the tampon was in place the aortic blood took on a venous hue. Whether the entire right bronchus or only the bronchus leading to the lower right lobe was occluded in each one of these trials was not determined, but from observations on the respiratory movement of the lobes, we believe the lower right lobe only was eliminated from ventilation in most of our trials.

In either event it is a very simple method of demonstrating how a certain proportion of unrespired blood going through the left auricle will produce cyanosis. In our clinical experience we usually see only the phenomena for which we have an interpretation. What we cannot interpret we fail to see. As our interpretation of cyanosis is improved and enlarged, cyanosis will be much more frequently recognized in clinical experiences.

In the study of respiratory phenomena of cardiorespiratory disease the role of moisture must be carefully interpreted. If we employ analyses of alveolar air for interpreting the partial pressure of oxygen and carbon dioxide in the circulating blood, such interpretations must predicate a uniform tonometric function of the entire respiratory area.

If areas of the respiratory membrane are eliminated from the respiratory function and other portions are normally functionating, then it is obvious that the respired air cannot be employed to interpret the partial pressure of CO_2 and oxygen in the blood. When the entire respiratory membrane is normally functionating then such interpretations are justifiable, but immediately the role of moisture in air spaces comes into play, or the air spaces of the lung are filled with an exudate without any change in the flow of

blood through the pulmonary vessels to the affected part, then there will be unrespired blood contributed to the aortic stream and analysis of respired air will give wholly unreliable interpretations of blood gases.

Summary. The significance of the foregoing observations lies in the recognition of dissociation between anoxemia and increased CO_2 content of the blood.

The CO_2 and oxygen content of respired air are measures of transpiration between blood and alveolar air only when the entire minute volume of blood passing through the pulmonary circulation is exposed to a respiratory membrane which has a uniform exposure to the ventilating air of the lungs. Normal subjects and patients with stenosis of the trachea or larynx will conform to these premises; so many patients who have respiratory symptoms from disturbed responses or altered control of respiratory rate and rhythm from the central or peripheral nerve supply to the lungs. But immediately the process of ventilation or blood flow is modified so uniformity of transpiration between the circulating blood and ventilating air is disturbed, then analyses of respired air cannot be employed to interpret the carbon dioxide and oxygen content of the blood.

FURTHER STUDIES ON ACTIVE IMMUNIZATION AGAINST DIPHTHERIA

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At two previous meetings I have reported the successful results obtained in immunizing children and adults against diphtheria.

Three injections of toxin-antitoxin conferred immunity upon about 97 per cent. of non-immunes for a period of at least two years. The children in a number of institutions are being tested every six months. This paper adds observations during an additional year. We find no decrease in the percentage of immunes. We have a few children who have remained immune for over three and one-half years. Drs. Zingher and Schroeder have given me the results in the following five institutions:

RESULTS OF RETESTS IN ACTIVELY IMMUNIZED CHILDREN

Institution.	Total tested.	Doses of toxin-antitoxin.	Months after injections.	Schick results.	Retest per cent. negative.
1. St. Agnes	20	1	20	18− 2+	90
	25	2	20	24− 1+	96
	12	1	8	5− 7+	41
2. St. Dominic	41	2	37	40− 1+	97
	43	3	37	43−	100
3. St. Joseph's	19	2	37	19−	100
	39	3	37	38− 1+	97
4. Leake & Watts	49	3	17	48− 1+	98
	15	3	6	11− 4+	73
5. Institute of Mercy	29	3	12	28− 1+	96

We have recently injected several hundred babies during the first ten days of life. The quantity of toxin-antitoxin was the

same as in adults. There was remarkably little reaction. Most careful observations showed no effect on the weight of the infants and in most no appreciable reaction could be observed.

It will be very interesting to note whether these injections give active immunity when given at this very early age and at a time when the infants have antitoxin derived passively from their mothers. My opinion as to the time at which persons should be immunized and the selection of subjects is as follows:

Vital statistics teach us that the greatest mortality from diphtheria is in the second year of life. The infant, at birth, possesses immunity transferred to it by its mother. By the end of six to twelve months it usually loses this protection. Sickness and death from diphtheria rapidly increase during the second six months. At the end of the first year a number of susceptible children begin to develop natural immunity and, in addition, their greater strength enables them to withstand the disease, so that the number of deaths which are highest in the second year of life gradually lessen from then on. Older children and adults, although they may develop a considerable amount of diphtheria, seldom die from the attacks, since antitoxin can be used in time.

With these facts before us it is easy to realize that when we consider the population as a whole, the most effective period in which to apply immunity is during the first six months of life. Fortunately, the fact that infants receive the injections with so little disturbance makes this probably the best period of life to receive them if the injections give immunity at this time.

It will undoubtedly be many years, even if our hopes as to the permanent persistence of active immunization are fully realized, before this method of treatment will be in general use. It is important for us, therefore, to consider under what conditions immunization should be carried out. In institutions where children are gathered together, immunization is of great value. At the Home for Hebrew Infants the active immunization of all children showing a positive Schick reaction has prevented the development of any case of diphtheria for three years, although before these injections were used there had been yearly epidemics with the accompanying loss of several lives. The fact that there

were during the first two of the three years a number of carriers of diphtheria bacilli among the youngest children adds to the proof that the prevention of diphtheria has been due to the immunizing injections. The practice has been to do a Schick test every three months and to only immunize the infants after they lost the immunity acquired from their mothers. This, probably, is the best practice for institutions where a bacteriologist is constantly on duty. Otherwise, it may be more sensible to inject all of the infants so as not to be liable to outbreaks occurring in those who have lost their passively acquired immunity. All school children should be given a Schick test, and those showing a positive reaction should receive an immunizing injection.

At the present time active immunization is being practised quite largely in the United States Navy and, to a considerable extent, in the Army. Although with antitoxin available death in an adult from diphtheria is rare and should never occur, nevertheless under the conditions in military service the presence of a few cases of diphtheria, with usually a number of diphtheria carriers on a vessel or in a concentration camp, creates a difficult situation to handle. By Schick-testing the men and giving the immunizing injections to those who react positively protection can be granted, and diphtheria made to cease within a period of two months as either a menace or an annoyance.

It should be noted that the development of immunity, either from natural means or through injections of toxin-antitoxin, or through injections of antitoxin, in no way prevents a person becoming a carrier, and that a carrier can, as any other individual, develop an ordinary follicular or croupous tonsillitis or pharyngitis. A case, therefore, that has a negative Schick reaction—*i. e.*, a person who possesses antitoxin and develops a suspicious throat and a culture shows diphtheria bacilli—is no more a case of diphtheria than a person developing similar lesions who has no diphtheria bacilli. In one case we have an infection from a streptococcus in a person who is a carrier of the diphtheria bacilli and in the other a person who is not. We are so apt to think that a positive culture in a suspicious throat proves that the lesions are due to the diphtheria bacilli lodged thereon that we forget that a carrier is just as apt to be infected

with pyogenic organisms as one who is not. Frequently in scarlet-fever patients in our hospitals croupous tonsillitis develops. Among these are some who have been immunized with antitoxin and others who are naturally immune, as shown by the Schick test. In all of these we realize that the individuals have antitoxin, and we find that without injections they recover just as well as with injections. We have never had a person with a negative Schick reaction develop the characteristic symptoms of diphtheria. It is certainly impossible for any person with antitoxin to be constitutionally poisoned by diphtheria toxin. Observations indicate that not even the superficial epithelium in these immune persons is poisoned by the diphtheria toxin made by the bacilli in carriers. It is absolutely proved that this does not occur to an extent which is characteristic of diphtheria. While a negative Schick test demonstrates that a person is safe, a positive reaction does not prove one is necessarily at the time susceptible, as there is, as in other infections, bactericidal immunity. The recovery in most cases of diphtheria is due to the development of bactericidal and not antitoxic immunity.

When there is doubt as to the certainty of there being a negative Schick test, antitoxin should be given in a suspected case.

SPLENECTOMY FOLLOWING RADIUM TREATMENT FOR MYELOCYTIC LEUKEMIA

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The first case of splenectomy for myelocytic leukemia was reported in 1866 by Bryant. His patient was in poor general condition and the spleen was very large; death occurred two and one-half hours after the operation. Bryant reported a second fatal case in 1867. The spleen in this instance was again very large and the general condition of the patient poor. Death occurred immediately after the operation.

The history of splenectomy for myelocytic leukemia is a repetition of the history of Bryant's cases and is extremely tragic. From 1866 to 1900 the operation was not infrequently performed. Approximately 86 per cent. of the patients on record died within a few hours of the operation. The patients for the most part were weak, toxic and anemic, with huge spleens and high leukocyte counts, and had insufficient vitality to respond favorably at a time when surgical treatment could be suggested and accepted. It is true that they were operated on at a time when least could be expected. The experience of different surgeons was similar and the conclusion naturally followed that splenectomy for myelocytic leukemia was in no sense a justifiable operation.

Bessel Hagen, in 1900, was able to collect 42 cases of splenectomy for leukemia in which 4 patients temporarily recovered. Johnston, in 1908, collected 7 cases that had been reported between the years 1900 and 1908, with the temporary recovery of two patients. The total number of splenectomies for leukemia to the year 1908 was therefore 49, with the temporary recovery of only 6 patients. It is known that of the 6 patients who withstood the operation, 4 died later. One lived as long as eight months, another lived three and

one-half years. From a practical standpoint, this experience meant a very prompt mortality of at least 96 per cent. Since the appearance of Johnston's paper the surgical treatment of myelocytic leukemia has received almost no attention. McCown (1915) reported 2 cases in which operation was done after preliminary treatment by means of arsenic and the *x*-rays. There was marked improvement in these patients three months after operation. The total number of cases reported in the literature to January 1, 1918, is therefore 51, with 8 temporary recoveries, an operative mortality of 86 per cent.; 4 of the 8 patients are known to have died later, giving a total known mortality of 93 per cent. Carstons has collected abstracts of all cases of splenectomy up to the year 1915. His article forms a complete and instructive resumé of the subject; he presents protocols of many of the published cases of splenectomy for myelocytic leukemia.

The remarkable remissions in the course of myelocytic leukemia, which can be produced by means of the exposure of radium element, or radium emanations over the enlarged spleen, have been recently discussed by Ordway, Peabody and the writer. The fact that the improvement following radium exposures occurred as a result of treatment over the spleen only and not over the long bones or over any other structures, led to the inference that possibly a malfunction of the spleen might have more to do with the general condition of the patient than had been supposed. Moreover, if the spleen could be removed at a time when it was small and freely movable, and when the general condition of the patient was good, the operative mortality would doubtless be much less than it had been formerly. Again, the elimination of the spleen as a mechanical factor would remove one of the most troublesome features of the disease and add to the patient's comfort. Naturally, in the light of the fatal former experiences, it was with considerable hesitation that splenectomy for myelocytic leukemia was resumed. The surgical treatment of leukemia has been discussed recently by W. J. Mayo and D. C. Balfour.

Report of Cases. In August, 1909, at the Mayo Clinic the spleen was removed in the case of a man, aged forty-five years (Case 27414), whose leukocyte count was 11,000 and whose differential

count showed no myelocytes. In August, 1911, two years later, the leukocytes were 64,500, with 14 per cent. myelocytes. The patient died December 27, 1914, five years and four months after the operation, with the symptoms of cardiorenal insufficiency. The spleen in this case weighed 2500 grams. This was evidently a leukemia of a more chronic type, as splenomegaly had been present four years preceding the operation. The total length of the history was, therefore, at least nine and one-half years. In view of the condition of the patient at the time of the operation it is possible that life was prolonged and the patient made more comfortable by splenectomy.

September 2, 1916, a spleen weighing 1100 grams was removed from a woman, aged fifty-six years (Case 171009). There had been no previous treatment by means of radium or the roentgen rays. The leukocyte count was 203,000, with 4.7 per cent. myelocytes. Thirteen days after splenectomy the count had become reduced to 47,400 with 15.7 per cent. myelocytes. The leukocytes rose to 113,600, with 36 per cent. myelocytes, two months after operation. The patient was in good general condition up to three hours prior to death, which occurred one year and three months after operation, and was probably due to cerebral hemorrhage. The total duration of the history in this case was approximately 3.5 years.

Twenty patients with myelocytic leukemia have been splenectomized at the Mayo Clinic. The two patients just discussed did not have preliminary treatment by means of radium. The remaining 18 patients, however, were treated by means of radium exposures over the spleen prior to splenectomy. The details of this method of treatment have been discussed in a former paper.[5] The spleen in each case of this series of 18 was very much reduced in size and the general condition of the patient was very much improved as the result of radium treatment. The 18 patients have been operated on within the last eighteen months; the last one January 21, 1918.

The operation itself has not proved difficult in cases of leukemia when the spleen was only moderately large; there have been few adhesions and but little embarrassment from hemorrhage. Postoperative complications have been absent save in one patient who died with peritonitis. Postoperative transfusion was necessary only once.

The operative mortality for the entire group of 20 cases was one death or 5 per cent. The operative mortality in the reported cases was 86 per cent. It is clearly demonstrated, therefore, that the operative mortality need not be high with proper preliminary preparation of the patient by medical means. A mortality of 5 per cent. is lower than the average for splenectomy in general. Patients in remissions with only moderately large spleens are not serious operative risks, even though they had formerly had various forms of hemorrhage.

Of the remaining 19 patients who recovered from operation, 9 have since died, from two months to one year and three months after operation (leaving out of account the early chronic case in which the patient lived five years and four months, with a total duration of history of nine years and six months). The total duration of history in 8 of the 9 fatal cases was from nine months to three years and six months. In 7 of the 8 it was more than two years.

The length of life following splenectomy seems to vary most closely with the total duration of the disease. Eight of the 9 patients dying subsequent to operation presented a duration of the disease of over two years, while 6 of 10 living patients presented a total duration of disease of less than two years. Two living patients have a chronic type of the disease, and present a duration of symptoms of over ten years and over six years, respectively. Aside from the chronic cases, then, when splenectomy has been performed there is no reason to infer that the disease runs more than its usual course of two or three years.

Seven patients were operated on early in the disease, that is, less than six months from the time of definite onset; 6 of these are alive, 5 are in excellent, or very good condition. It is possible, though not likely, that in these early cases the results will be better than in the later ones; 4 of the 6 patients have already lived more than one year. Nothing, however, of a definite nature can be inferred from the fact that 6 of the 7 are alive, inasmuch as the total duration of the disease in all of them is less than two years.

It is worthy of note that in 2 cases of a chronic type the patients are alive ten months, and one year and seven months, respectively,

after splenectomy. The total duration of disease in these two patients has been six years and ten months, and ten years and seven months, respectively. The spleens were large and fibrous and the leukocyte counts were not very high. Indeed, splenectomy may prove warranted in the very chronic types of the disease, from the standpoint of the patient's comfort, even though it be ineffectual in the prolongation of life.

The ages ranged from 24 to 56 years and seemed to make no difference in mortality. In general, patients with the largest spleens at the time of operation have died first. This would probably indicate that these patients represented a more severe type of the disease. The average weight of the spleens of the patients who were first treated by radium, and who have died since splenectomy was performed, was 975.6 grams. On the other hand, those with the smallest spleens at the time of operation have, in general, lived the longest. The average weight of the spleens of these patients was 722.5 grams. Of 12 patients who lived one year or more after splenectomy, the average weight of the spleen at the time of operation was 800 grams; in 9 patients who had had a very thorough course of radium treatment, it was 498.3 grams.

A period of improvement in the patient's general condition followed operation in all cases save 3. This general improvement consisted of a feeling of well being which may have been psychical, of an improvement in the appetite and the anemia, of a gain in weight, and a definite loss of the icteroid tint when it was present. The general condition in most instances was quite satisfactory before operation so that one cannot say definitely that splenectomy was the factor responsible for immediate improvement. Marked gain in weight was, however, almost a constant postoperative feature. The period of improvement was not of definite duration.

The blood, after splenectomy, showed no definite alteration, with the exception of an increase in the relative percentages of both small and large lymphocytes. This was apparently not secondary to the fluctuation of the leukocyte count itself. Its significance is undecided and the characteristics of these mononuclear cells require further study. It is to be learned whether they are of bone marrow origin or whether splenectomy in reality stimulates the activity of

lymphopoietic structures. In some instances there is a very marked decrease, temporarily in the number of myelocytes found after splenectomy.

Two patients returned for observation after operation and on examination were found to have enormously enlarged livers which, however, gave no discomfort. The general condition and color were quite good in one of them.

One patient (Case 180499) who died two months after operation, and who had presented very slight enlargement of the glands, developed a remarkable glandular hypertrophy immediately after the operation, which persisted to the time of his death. The leukocyte count rose to 466,000, of which 63 per cent. were small lymphocytes and 18.7 per cent. were large lymphocytes, with only 3 per cent. myelocytes. Before operation the small lymphocytes were as low as 3 per cent. with 28.3 per cent. myelocytes. The small lymphocytes rose steadily, however, after radium treatment, to the time of operation when they were 39 per cent. with 0.3 per cent. myelocytes. Two weeks after operation, the small lymphocytes rose to 61.7 per cent., and the case if then seen for the first time, would doubtless have been diagnosticated as a lymphatic leukemia. Examination for oxidase granules in these cells was not made. A gland examined microscopically after death showed lymphocytic hyperplasia. A detailed conception of the results following splenectomy may be obtained from an examination of Tables 1 and 2.

TABLE I.—SPLENECTOMY FOR MYELOCYTIC LEUKEMIA.

Case.	Age.	Sex.	Leukocytes time of operation.	Date of operation.	Weight of spleen.	Death time after operation.	Duration of disease.
				Operative mortality.			
216648	36	F.	22000	1-21-18	1705	6 days	1 yr.
				Subsequent mortality.			
27414	45	M.	11000	8-11-09	1514	5 yrs. 4 mos.	9 yrs. 6 mos.
171009	56	F.	203000	9- 2-16	1100	1 yr. 3 mos.	3 yrs. 6 mos.
173772	35	M.	7800	12- 8-16	740	1 yr.	2 yrs. 6 mos.
175791	24	F.	9000	1-18-17	750	4 mos.	2 yrs.
176684	26	F.	13200	2-28-17	560	1 yr. 2 mos.	2 yrs.
162899	32	F.	37900	3- 8-17	1000	3 mos.	9 mos.
188262	50	F.	22000	4-10-17	1340	8 mos.	3 yrs.
180499	42	M.	5600	5-11-17	1300	2 mos.	2 yrs.
204838	53	M.	11400	8-17-17	410	3 mos.	2 yrs. 3 mos.

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TABLE II.—SPLENECTOMY FOR MYELOCYTIC LEUKEMIA.

Case.	Age.	Sex.	Leukocytes time of operation.	Date of operation.	Weight of spleen, grams	Condition.	Time after operation.	Duration of disease.
				Subsequent	condition of living	patients.		
168742	46	M.	16400	9-19-16	2500	Good	1 yr. 7 mos.	10 yrs. 7 mos.
173312	33	M.	3800	11-24-16	890	Excellent	1 yr. 6 mos.	2 yrs. 6 mos.
160937	37	F.	68000	12-13-16	338	Good	1 yr. 5 mos.	3 yrs. 5 mos.
175574	37	M.	15200	1-13-17	500	Excellent	1 yr. 3 mos.	1 yr. 5 mos.
169876	36	F.	8400	1-27-17	220	Fair	1 yr. 3 mos.	1 yr. 6 mos.
177183	28	F.	54400	2-17-17	440	Good	1 yr. 2 mos.	1 yr. 8 mos.
181494	19	F.	7500	3-15-17	410	Excellent	1 yr. 1 mo.	1 yr. 7 mos.
186558	50	F.	7200	4- 9-17	387	Good	1 yr.	1 yr. 6 mos.
193829	29	M.	17000	6- 4-17	1320	Good	10 mos.	6 yrs. 10 mos.
199386	29	F.	26000	7-26-17	220	Excellent	9 mos.	11 mos.

May 1, 1918.

SUMMARY. 1. Twenty patients with myelocytic leukemia have been splenectomized; 18 of them after preliminary treatment by means of radium exposures over the spleen. The spleen and the leukocyte count were, by means of radium, very much reduced and the general condition of the patients was greatly improved.

2. One patient died, an operative mortality of 5 per cent. The operative mortality of cases reported in the literature in which little or no preliminary medical treatment had been given was 86 per cent.

3. Ten of the 20 patients are living in good general condition from nine months to one year and seven months following splenectomy. However, these patients have not yet outlived the life expectancy for the disease.

4. Of 7 patients operated on within six months of the time of the onset of the disease, 6 are alive.

5. It is probable that at least in certain chronic types of myelocytic leukemia with fibrous spleens and relatively low leukocyte counts, splenectomy may be justifiable for the comfort of the patient.

6. A review of the cases at this time reveals no evidence that the *duration* of the disease is altered in any definite way by splenectomy.

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CHRONIC MYOCARDITIS: A CLINICAL STUDY

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Notwithstanding the insistence of many internists and the very great interest in functional disturbances of the cardiac mechanism aroused by the information obtained from the use of the polygraph and electrocardiograph, there is still a marked tendency among physicians to stress unduly the importance of valve lesions of the heart. If one glances through the systems and text-books of medicine one gains the idea that various forms of valve lesions originating from chronic endocarditis form the chief cause of cardiac disease. The diagnosis and treatment of valve lesions bulk large in the chapters devoted to heart disease.

Scattered through the pages there is ample evidence that muscle function in last analysis determines cardiac efficiency or inefficiency and various forms of chronic degeneration and interstitial inflammation of heart muscle are described. However, there rarely appears a clear description of a very common type of chronic cardiac disorder in which the fault is primarily in the heart muscle and the valves themselves are normal.

In just the same way text-books of pathology fail to give any definite satisfactory description of this very common type of cardiac lesion, probably because very often, as we shall see later, the heart muscle and the coronary system present no lesion that the pathologist can describe in objective terms.

A possible reason for this condition lies in the fact that usually the type of case which I have in mind is merged with cases of organic mitral lesion under the heading "mitral insufficiency." This results from the fact that with myocardial disturbance there

is in most cases a mitral regurgitation from stretching of the mitral orifice, and such cases usually, though not always, have a systolic murmur at the mitral area.

I do not mean to imply that this type of case is not recognized, for it is, but its frequency and importance are not emphasized adequately. It is not likely that I will add any new data to the clinician's store of information. What I wish to do is to emphasize the relative importance of a group of cases in which primarily the heart muscle fails and in which the valves are intact in the sense of showing no organic lesion. In describing my own experience with them I may be able to change the views usually held of the relative importance of different types of cardiac disease and bring out a somewhat clearer conception of what in my experience is a very frequent type of cardiac disease.

Such cases will be spoken of as cases of chronic myocarditis. This is the term commonly used, but it is a poor term, for it implies inflammation, whereas degeneration in the heart muscle often is found. Still worse for the term, frequently the pathologist can find no signs of inflammation or degeneration. However, if we understand what is meant by the term it does not make very much difference after all if it is a poor term in an etymological sense, and had I a satisfactory term to suggest, it is not probable that it would be adopted for general use, for new terms are accepted very grudgingly.

As I understand the present-day clinical usage of the term chronic myocarditis, it means a group of cases in which the heart has failed to function properly, and the patient has the symptoms and signs of cardiac insufficiency or decompensation. The disturbance is muscular, for the valves show no organic change. Sometimes at death an increase in interstitial connective tissue is found; at other times the heart muscle shows degeneration of varying type; not infrequently the pathologist is unable to find either in gross or after microscopic study any lesion in the heart muscle. Sometimes the coronaries are sclerosed; in other cases they are normal. Not infrequently the pathologist finds no cause for the cardiac failure.

You will recall that Cabot, in a correlation of clinical and patho-

logical diagnoses, said that in 52 per cent. of the cases diagnosed during life as chronic myocarditis no such lesion was found at autopsy, and in only 22 per cent. did the clinical and pathological diagnosis agree. To my mind this merely means that clinician and pathologist talked a different language and their terms could not be compared. The patient was dead, died because the heart muscle failed to do its work. The clinician calls such a condition myocarditis, not meaning necessarily inflammation of the myocardium. That the pathologist cannot find any lesion in the heart muscle does not prove the soundness of the muscle but merely the inadequacy of the methods of pathology in so far as they fail to show cause for a functional defect.

According to Cabot, many mistakes are made in the clinical diagnosis of chronic myocarditis when the clinical work is checked by the pathologist. In my own experience, from a clinical study of the patient, there are few conditions in which mistakes are made so seldom by us as in this group of cases, in which before autopsy I can say this is a case of chronic myocarditis, meaning thereby cardiac failure due to myocardial insufficiency without organic valve lesion and in which I prophesy that the pathologist will find an enlarged heart, with valves showing little or no chronic endocarditis, *i. e.*, no thickening or distortion, and the various viscera will show changes subordinate to or secondary to the cardiac failure. Sometimes the heart muscle will show lesions; at other times not even microscopic study will reveal any. Sometimes the coronary arteries will be markedly sclerosed; at other times they will seem normal. The lesions found in the heart are not at all constant. I was once a pathologist myself, and so the pathologists may pardon my saying that they can offer no satisfactory explanation in an objective sense of what has been observed at the bedside—namely, cardiac failure. Thirteen years ago, as a pathologist, I could not satisfy the curiosity of the clinician; today the pathologist and the pathological literature are unable to answer my query, Why has the heart failed?

Now let me turn briefly to my clinical experience. As to frequency of such cases, in 1917 in my wards at the Peter Bent Brigham Hospital I studied 230 cases of chronic cardiac disease. Of these, 120

were positively diagnosed as chronic myocarditis and 5 questionably so, while 105 were regarded as cases of chronic valvular disease. Of course, in the 105 patients with chronic valvular disease many had myocardial insufficiency, but this is included in the diagnosis, chronic cardiac valvular disease, and the term chronic myocarditis is used only for the patients with cardiac insufficiency in whom we believe there is no organic valve lesion. In 1916 the figures were proportionately the same, 156 positively diagnosed chronic myocarditis and 141 chronic cardiac valvular disease; in 1915, 91 and 113 respectively, in three years a total of 367 chronic cardiac cases without organic valve lesion and 359 with organic valve lesion. The diagnosis of simple or uncomplicated mitral insufficiency of organic origin is made relatively infrequently; in 1917, 10 cases, including 3 doubtful ones out of a total of 105 with organic valve lesion; in 1916, 24 cases, with 7 doubtful ones out of a total of 141; and in 1915 a total of 28 out of 113. These figures show an increasing conservatism with regard to diagnosing organic mitral insufficiency. So you see that, looking upon chronic cardiac disease from the viewpoint that I have expressed above, in a general adult medical clinic we see rather more patients with the symptoms of chronic cardiac disease who are suffering from chronic myocardial disturbance without organic valve lesion than those who show signs of organic valve lesion.

Perhaps our clinic may be unduly conservative in regard to making the diagnosis of mitral insufficiency unaccompanied by stenosis. As I have already stated, postmortem examination usually has agreed with the bedside diagnosis in this respect. In 42 autopsies clinically of this group the pathologist described very slight thickenings of the mitral valve in 5 and considerable thickening in 5, while in 32 the valve flaps were not thickened and the valves seemed in every way normal. Moreover, a study of all of our postmortem material without any reference to antemortem diagnosis confirms the view that organic mitral disease in older people is relatively infrequent and when it does occur there is present usually stenosis as well as insufficiency. Dr. Levine, a former assistant,[1] analyzed from our records 247 con-

[1] Am. Jour. Med. Sc., 1917, cliv, 43.

secutive postmortem examinations with reference to organic mitral lesions; 107, or 41 per cent. of these patients, were over fifty years of age, and of these but 2 had definite chronic mitral endocarditis, while of 154 under the age of fifty, 21 had definite chronic mitral endocarditis. This is further justification for conservatism in diagnosing pure mitral insufficiency of organic origin, particularly in older people in whom, as we shall see later, chronic myocarditis occurs oftenest.

Since the opening of the Peter Bent Brigham Hospital in the spring of 1913 up to January 1, 1918, we have had for study 407 patients in whom we considered that a cardiac insufficiency was of myocardial origin without organic valve lesion; in the sense of our definition, cases of chronic myocarditis. Of these 240 were males and 167 females; 115 of these were in the hospital more than once and many remained in the wards for long periods of time. In all but relatively few there was ample opportunity for careful study of the cases. According to age incidence the largest number came in the decade fifty-one to sixty (143 cases). In the preceding and succeeding decades the number was smaller, but about the same number occurred in each of these decades as shown in Table I. All but 41 occurred in patients over forty years of age.

TABLE I

Age at admission.	Male.	Female.	Total.
Below 30	5	4	9
31 to 40	17	15	32
41 to 50	53	40	93
51 to 60	84	59	143
61 to 70	52	34	86
Over 71	29	15	44
	240	167	407

As to etiology the relation of rheumatism and of syphilis is of interest. Of the total of 407 patients, 112 (74 males and 38 females) gave a history of an antecedent rheumatism. Of these the time relation of the rheumatism to the onset of symptoms was as follows: 59 had had rheumatism within ten years of their admission for cardiac disease while 30 had it twenty-five or more years beforehand. The age of the patients when they had rheumatism was as

follows: one to ten years, 3 cases; eleven to twenty, 10 cases; twenty-one to thirty, 16 cases; thirty-one to forty, 22 cases; forty-one to fifty, 21 cases; fifty-one to sixty, 23 cases; sixty-one to seventy, 10 cases; seventy-one or more, 6 cases. It is to be noted that 60 out of 112 cases who gave a history of rheumatism were over forty years of age when they had rheumatism. This makes it improbable that many of these were patients with acute rheumatic fever. Rather it indicates that of those giving a history of rheumatism more than half in all probability had the arthralgia or chronic arthritis so common in later adult ages. This view is further borne out by the fact that of those admitted to the hospital on account of the cardiac decompensation of chronic myocarditis over the age of fifty, 29 out of 39 had their rheumatic symptoms within five years of their admission and many of these a very short time beforehand. Few if any of these could have had acute rheumatic fever. Making these deductions it seems probable that only relatively few of our patients with chronic myocarditis could have had acute rheumatic fever, and so rheumatism in this sense played but a small part in the etiology of this group of cases of chronic myocarditis.

As to syphilis, in order to have constant criteria the Wassermann reaction has been taken rather than a history of syphilis. The possibility of failure to include those who have had syphilis as judged by history and the possibility of error of observation in the technic of the Wassermann reaction is recognized fully, but, on the whole, the Wassermann reaction would seem to offer the best grounds for estimating the importance of syphilis as an etiological factor in these cases. Of a total of 369 patients in whom the reaction was tested the Wassermann reaction was positive in 35 and negative in 334. In only 38 patients was the reaction not tested. The small number of patients with positive reaction is very striking when it is recalled that these were in large part public ward cases among whom the incidence of syphilis as measured by a positive Wassermann reaction is large. In fact, this percentage in our chronic myocarditis patients is a little less than the average incidence of syphilis for all admissions to our wards, and so this incidence of syphilis might be regarded as coincidence. Certainly,

the figures indicate that syphilis has played a very small role in the etiology of this group of cardiac cases which seems very surprising when it is recalled how extensive a part vascular lesions play in the syphilitic process.

Alcohol has been suggested as a cause of myocardial insufficiency. In our cases 239, or slightly more than half, admitted the use of alcohol, and in 111 of these there appears to have been a pretty chronic use of alcohol. In those admitting the use of alcohol over long periods, directly or indirectly, the alcohol may have been a causative factor. Of this there is no definite proof. If a causative factor it explains slightly more than one-third of the cases. As to its real significance in the group I feel doubtful.

Disturbances in thyroid activity most certainly lead to myocardial disturbances. However, goitre or history of hyperthyroidism was extremely infrequent in our cases and could have been a cause in extremely few of them.

Another factor in producing this condition that should be considered is hypertension. We found the systolic pressure 150 or lower in 148 patients, from 150 to 170 in 72 and over 170 in 178 out of 398 cases, in whom satisfactory blood-pressure observations were recorded. So far as etiology of the cardiac failure is concerned, hypertension can play a part in considerably less than one-half, for it is not likely that a pressure under 170 would be of any great significance in producing myocardial insufficiency and myocardial lesions from overwork. Even in these patients, in some at least, hypertension is probably a coincident not a causative factor in the cardiac breakdown. Anyhow, hypertension cannot be regarded at most as a very common cause of chronic myocarditis, though it may be expected in a considerable proportion of the cases.

Chronic nephritis had been looked upon as a causative factor in chronic myocarditis. Undoubtedly in some cases of hypertension the primary cause of the high blood-pressure lies in a chronic renal lesion, and in such the renal lesion may be considered as a causative factor in the myocarditis. However, as our functional studies of the kidney have shown, very often the hypertension is primarily of vascular origin and the renal lesion is secondary to

the high blood-pressure and underlying vascular lesion. Then in other cases renal and myocardial disturbance may have a common cause. Again, it is not easy to say in a given patient with myocardial insufficiency whether nephritis exists or not. Very often casts and albumin will be found, but their origin may be in large part in the chronic passive congestion of the kidney. In our experience very often these patients, with decreased urinary output, albuminuria and cylindruria, show a marked degree of renal efficiency, as indicated by the phthalein excretion and by diuretic response to stimulation. That such a kidney shows enough nephritis to have been a factor in the etiology of the chronic myocarditis seems improbable. Examination of our records shows that in 202 of the total of 407 patients with chronic myocarditis there seemed enough renal disturbance to justify the diagnosis of chronic nephritis. However, my opinion is that in many of these the renal lesion was secondary to or coincident with the cardiac rather than causative. Our postmortem examinations usually have revealed a type and extent of renal lesion that is in accord with this view. In 17 out of 41 autopsies the kidneys were free from chronic nephritis, though showing chronic passive congestion. In 9 out of the 41 the kidneys were of the arteriosclerotic type, while in only 15 was there definite chronic nephritis. In only this last group would it seem likely that the renal lesion could have had any causal relation to the cardiac, and even in these the two processes well might have been coincident.

The incidence of arteriosclerosis in the group is more difficult to judge. For its determination we have available routine observations of peripheral arteries, often only the radial. However, it is recognized that arteriosclerosis is of irregular distribution and may be present in one group of vessels and not in another. Unless it is accompanied by hypertension it would not seem probable that sclerosis elsewhere than in the coronary arteries could have much influence on the heart muscle, and its presence in peripheral vessels is too unsatisfactory an indication of coronary sclerosis to help in forming a judgment as to the condition of the coronaries. So it hardly seems of value to tabulate clinical observations on peripheral arteries as evidence of the condition of the coronaries. However, of these cases 43 came to autopsy, and o

these 21 showed quite definite coronary sclerosis, in 9 of which it was moderate and 12 marked, while in 22 the coronary vessels were relatively normal, *i. e.*, showed no sclerosis or only a few patches of moderate change.

Overeating, with resultant overweight or a pathological obesity, usually is considered a possible causative factor in this type of heart disturbance. In our group of cases 188 out of 393 patients appear to have been overweight, and of these a considerable number were obese. From these figures it appears that a little more than one-half of the patients were not fat in any sense of the word, and quite frequently these patients were of the thin type. My impression is that obesity is not marked enough to have been a possible causative factor in more than one-third of these cases studied at the Brigham Hospital, and in these, of course, it may have been only coincident.

The role played by focal infection in causing myocardial disturbances is uncertain. Many, very many in fact, of these patients had had bad teeth with marked pyorrhea alveolaris and decayed root stumps, and undoubtedly alveolar abscesses were common. We are only too familiar with the rotten mouth conditions of our ward patients whatever their disease. Bad teeth are common enough in the myocarditis patients to be an important causative factor, but they are so common in all hospital patients that I feel skeptical as to their etiological relation to the myocardial group.

In the heart muscle the pathologist found an interstitial connective-tissue increase in 27 out of 40 hearts carefully described. Here examination was not exhaustive enough to exclude smaller foci of connective-tissue increase, and in the 27 in which it was found, the connective tissue very often was only moderately abundant or the definite patches occupied only a small part of the myocardium. In 8 hearts the muscle seemed normal, while in 4 only moderate fatty degeneration was seen. In one case amyloid degeneration was present.

Electrocardiography is an important method of determining cardiac disturbances which indicate myocardial lesions, either functional or organic. In the 407 cases of this group, electrocardiograms were made on 328 patients, with the following results: 30 patients showed normal curves; simple left-sided preponderance

occurred in 83 patients and right-sided in 10; 38 patients showed left-sided preponderance, with premature or ectopic contractions, oftenest having origin in the ventricles, while only 1 showed right-sided preponderance with ectopic beats. This is as might be expected, 111 with left-sided hypertrophy in contrast with 11 showing right-sided hypertrophy; 16 cases had ectopic beats without showing the complex of either left or right-sided muscle preponderance.

Auricular fibrillation occurred in 96 and auricular flutter in 9 patients. In these, with very few exceptions, left-sided muscle preponderance occurred. In many ectopic beats were also present. In 41 cases the electrocardiogram showed the widened or distorted ventricular complex indicating disturbance in the conduction mechanism, either block in the right or left main stem or more probably degeneration changes involving smaller subdivisions of the conduction system. Here only more marked changes in the ventricular complex are counted. Slighter degrees of widening or distortion of ventricular complexes occurred in other patients, and these are undoubtedly of considerable significance, but they will be discussed in another paper by Dr. Howard F. West.

Paroxysmal tachycardia occurred once, paroxysmal ventricular tachycardia once and sino-auricular block once. In 2 cases complete auriculoventricular block was the chief disturbance noted. The patients with auricular fibrillation, auricular flutter and distortion of the ventricular complex, 146 in all, represent from an electrocardiographic viewpoint the patients with the most serious muscle disturbance, and they form a considerable proportion of the total of 328 studied electrocardiographically. The finding of these changes in the electrocardiogram helps in the diagnosis of the type of case, but it is evident from our figures that often the electrocardiogram shows no change indicative of serious myocardial disturbance even in patients with badly decompensated hearts, for almost every one of our patients was of the type requiring hospital bed treatment, and so represented advanced stages of the disease. Unfortunately, our records do not contain enough polygraphic tracings to justify any opinion as to the frequency of pulsus alternans in this group of cardiac disturbances.

Physical signs in these patients are quite characteristic, though

there are no pathognomonic signs. The heart is usually enlarged, often markedly so. Hypertrophy is by far oftenest of the left ventricle. Cardiac sounds are not characteristic. Gallop rhythm and tic-tac quality are found, but frequently they do not occur. A systolic murmur is frequent, usually loudest at the apex. It varies all the way from a soft blowing murmur to a loud harsh or musical one. In some cases no murmur is heard. In my opinion the quality or intensity of the murmur is no criterion as to whether there is an organic valve lesion or merely a dilated valve orifice. In the same way transmission of the murmur is of no significance. Given an enlarged heart and any sort of a systolic murmur at the apex in a patient over forty, with decompensated heart, the probability of there being an organic mitral insufficiency is very small. The systolic murmur is the least significant physical sign, in my opinion, in this group of cases. The apex impulse usually is diffuse, often not forcible. Very often there is a marked discrepancy between visible pulsation and the palpable heave of the apex region. It is surprising sometimes to feel so weak a thrust from a heart markedly enlarged and to the eye beating forcibly. With the heart condition go the signs of decompensation, chronic passive congestion of the viscera and edema.

X-ray silhouette of the heart is not characteristic. Most often it shows well the left-sided enlargement. A number of times I have seen the heart shadow of a globular form, and these hearts sometimes are diagnosed as pericardial effusion by the roentgenologist.

With rest in bed and digitalis these patients can make most surprising improvement. It is a group in which digitalis is very efficient whether auricular fibrillation is present or not. Diuretics here have their most efficient action. A waterlogged patient of this group may lose 20, 30, 40 or even 60 pounds of fluid in a week's time and have most of his symptoms disappear. Of course, there is a marked tendency for them to recur, especially after return to work, and with recurrence cardiac response to digitalis becomes less until the stage is reached, when, under digitalis, the heart progressively deteriorates and no therapy will stay the progress of the disease.

As to what really produces this type of cardiac insufficiency we

are ignorant. Various theories have been advanced to explain how minor lesions by position might lead to serious cardiac disturbance. After critical examination these theories, however, seem unsatisfactory. Our clinical studies fail to show any constant cause, and in some cases, even after careful pathological study, the condition of the heart remains inexplicable. Further study of these patients during life and after death is certainly needed before we can have any adequate understanding of the mechanism and the causes of the condition.

Summary. To summarize, there is a very common chronic cardiac condition in a general hospital for adults equal in frequency of occurrence to chronic valvular disease of the heart, which for a better term may be called chronic myocarditis. By this term is meant cardiac insufficiency from myocardial disturbance without organic lesion of the heart valves. A very large proportion (266 out of 407) of these patients are, on admission to the hospital, over forty years of age—rather more are men than women. The heart is enlarged nearly always—usually there is a systolic murmur at the apex—but whatever its intensity or transmission it is very rare to find any thickening or distortion of the valve flaps or chorda tendinæ. Acute rheumatic fever and syphilis both are relatively uncommon in these cases, and neither play any considerable part in the etiology. Chronic use of alcohol occurs in about one-third of the cases. High blood-pressure is often found, but is absent in more than half of the cases. Chronic nephritis is often present, as is hypertension, but in 17 out of 41 cases at autopsy the kidneys showed no chronic nephritis. Coronary sclerosis is an important factor in only about half of the cases. Interstitial connective-tissue increase is the lesion most found in the heart muscle, but in numerous cases the heart muscle seems practically normal except for hypertrophy of the fibers. Electrocardiography often gives evidence of disturbed muscle function, about half the cases show auricular fibrillation or flutter, or the distortion of the ventricular complex indicating some disturbance in the conduction system; but in even advanced cases the electrocardiogram often shows no significant disturbance. Digitalis in the earlier breaks in compensation is a very efficient drug, and diuretics produce marked diuresis.

ROCKY MOUNTAIN SPOTTED FEVER, PATHOLOGY AND ETIOLOGY

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The first steps taken in this study of Rocky Mountain spotted fever, begun in January, 1916, were directed toward determining the nature of the disease. The results obtained in guinea-pigs and monkeys were later, in the spring of 1917, confirmed in three human cases. Since then two additional human cases have been studied and the disease in rabbits has been investigated.

The pathology in man and in laboratory animals is essentially the same and may be defined as a specific infectious endangitis of the peripheral bloodvessels. The writer knows of no other human disease so exactly duplicated in animals, irrespective of the mode of inoculation, whether by injection of blood from an infected animal or through the bite of an infected tick (Dermacentor venustus, Banks). The arteries, veins and capillaries of the skin and subcutaneous tissues, and in the male in the testes and appendages are chiefly affected. The visceral bloodvessels very rarely show lesions; more commonly there are lesions in the vessels of the skeletal muscles and thyroid gland.

The earliest lesion in bloodvessels is a collection of large mononuclear phagocytic cells (endothelial cells) over an area of swollen and degenerated endothelium of the intima. Hyaline change of endothelial cells and smooth muscle cells of the media occurs, and in response to this the presence of polymorphonuclear leukocytes. The lesion, however, is essentially a proliferative lesion, and extensive concentric thickening of vessels is often found, due to accumulations of endothelial cells in and upon the intima. Thrombosis

usually occurs as a result of these lesions both in laboratory animals and in man. In the former necrosis of the skin of the scrotum, of the paws and of the ears is common. In man a petechial rash is the rule and frequently necrosis of the skin of the scrotum and prepuce. Minor histological changes observed in man surrounding bloodvessels and involving nerves explain the extreme hyperesthesia of spotted fever patients.

In the lesions in endothelial cells in the intima and in smooth muscle cells in the media there is found a minute microörganism which can best be demonstrated in sections stained by a slightly modified Giemsa technic. The parasite may be demonstrated in mammalian and tick tissues by the same technic.[1]

They can also be demonstrated in sections stained with eosin methylene blue and in sections overstained with Loeffler's methylene blue and decolorized with dilute acetic acid. The organisms can also be found in smear preparations of material obtained by scraping and teasing the under surface of the skin from locations showing lesions.

In man and laboratory animals the organisms occurs in sections as minute rods in pairs often lanceolate and surrounded by a clear zone or halo. In size they are much smaller than the influenza bacillus, probably not over a third as large. In smear preparations from guinea-pigs, lanceolate paired forms, minute rods with irregular staining and rods with chromatoid granules have been

[1] (1) Perfect fixation in Zenker's fixative saturated with corrosive sublimate. For ticks it is best to omit the acetic acid. (2) Paraffin embedding: Sections should not be over 4 microns thick to ensure good staining with Giemsa's stain. After treatment with iodin for the removal of sublimate deposits the sections should be treated for ten minutes in 0.5 per cent. solution of sodium hyposulphite, which must be removed by thorough washing and a final change of distilled water. (3) Stain twelve to eighteen hours, changing the solution twice in the first two hours in the following:

Giemsa's stain	60 drops
Reagent methyl alcohol	3 c.c.
0.5 per cent. sodium carbonate	4 drops
Distilled water	100 c.c.

(4) Without washing in water differentiate in 95 per cent. alcohol until excess of stain is removed. Dehydrate quickly, clear in xylol or benzol and mount in oil of cedar wood.

Formula used for Giemsa's stain:

Azur II eosin	3.0
Azur II	0.8
Reagent glycerin	125.0
" methyl alcohol	375.0

found. A very striking feature in sections in all types of material is the close packing of the organism in smooth muscle cells of the media of vessels. The parasite has been found in all of the five human cases, in scores of guinea-pigs, numerous rabbits and in each of four monkeys inoculated.

The parasites are easily found in ticks which have been allowed to feed on infected animals. The most accurate method of demonstrating them is in sections, although they can be found in smear preparations in the organs of ticks. In the present work the method of study in ticks has been to remove the dorsal plate of the tick and to take from one side salivary gland, Malpighian tubule, leg muscle and a portion of the intestinal tract for smear preparations. The remainder of the organs were removed in one mass for embedding in paraffin and serial section. Giemsa's stain was used both for the staining of smear preparations and sections. The tissues were fixed in Zenker's fixative without acetic acid. Approximately 200 ticks have been studied by this method and the material may be divided into the following groups: (1) adult ticks fed upon infected animals and then proved to be infective; (2) adult ticks proved to be non-infective by feeding on normal animals; (3) wild adult ticks, including partially engorged ticks from horses and cattle and unfed adult ticks obtained by dragging; (4) nymphs from uninfected strains fed upon infected guinea-pigs and later proved to be infective; (5) nymphs fed upon guinea-pigs and proved to be non-infective. In the course of these experiments a substantial contribution to the transmission of the disease by the tick has accumulated. The laborious nature of the experiments was justified because of the impossibility of cultivation of the parasite.

In the examination of these ticks in no instance were the parasites found in proved non-infective ticks or in nymphs from a proved non-infective source fed upon normal guinea-pigs. In every instance the parasites were found in proved infective ticks. In a very few instances it was impossible to infect ticks by feeding on infected pigs, and in these cases where the tick did not transmit the disease the parasites could not be found. The results prove that this parasite is inseparable from ticks capable of transmitting

the disease. The parasite as found in sections of ticks exhibits the following forms: (1) a lanceolate paired form similar to those seen in mammals; (2) a smaller more slender rod-shaped form; (3) a minute oval-coccoid form just within the limits of vision characteristically packed within nuclei of epithelial cells and in muscle cells of the intestinal tract. In smear preparations these various forms can be identified and in two experiments where infected nymphs were examined each day after feeding a certain sequence in the morphological types occurred which is of possible significance in tending to the conclusion that the parasite is not an ordinary bacterium and that it probably represents a new type of microörganism. Apparently only the larger lanceolate type is to be found in ticks which have been kept for several months. The occurrence of the parasite in abundant numbers in the salivary glands indicates that the infection occurs through this route.

This parasite was unquestionably seen by Ricketts in infected animals and in human cases. He was led to erroneous conclusions by the confusion of certain small bacteria found in normal ticks with this organism. In the course of present research, bacteria of various morphological types have frequently been found in wild ticks and in the ova of wild ticks. One bacterium commonly present because of its small size can be mistaken in casual observation for the larger form of the spotted-fever organism.

The following conclusions have been arrived at: The specific lesions of Rocky Mountain spotted fever are practically restricted to the bloodvessels of the skin and genitalia. The reaction is a characteristic one, an endangitis characterized by endothelial cell proliferation, local necrosis of endothelium and smooth muscle and thrombosis.

The cause of the disease is the minute parasite described. The parasite in all probability represents a new type of microörganism. A complicated life cycle has been excluded and the organism seems to be most closely related to the bacteria rather than to protozoa.

A STUDY OF EIGHTY CASES OF EMPYEMAS AT CAMP UPTON

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Even a very casual observation of the cases of empyema which have appeared in the Base Hospital at Camp Upton during the past winter and spring shows that we are dealing for the most part with an altogether different type of this disease from that to which we are accustomed. The very early appearance of this complication in the course of pneumonia, its unusual bacteriology and the very high mortality which accompanies it, even under favorable conditions, are the most striking and important variations. Closer study indicates a different train of symptoms, certain alterations in physical signs and a modified pathological picture while operative procedures, which when resorted to in ordinary empyemas give almost uniformly good results, have in this epidemic been attended by so high a death-rate as to cause both physician and surgeon to question seriously its advisability, value and type.

In view of these deviations from the usual in this frequent cantonment infection a close study of all cases was imperative. In this problem it was at once apparent that closely associated laboratory and clinical methods must be constantly applied and a large portion of the work of the medical and laboratory staff of this hospital has been devoted during the past winter to this insis-

tent problem. This study has been a conjoint clinical and laboratory one, far more than is usually the case, for it has been found absolutely necessary that the laboratory staff follow the clinical aspects of the cases, even to the point of studying the physical signs, and a proper clinical comprehension of the individual case has been found inseparably connected with the work in the laboratory.

Analysis of the clinical picture and the laboratory findings soon showed us that we were dealing with a specific and virulent infection by an organism which is rarely encountered in civil infections of the lung and pleura. In most of these cases the organism in question—the so-called Streptococcus hemolyticus—has been the causative agent not only of the empyema but of the pneumonia associated with it. The relation between streptococcus pneumonia and the incidence of empyema is well shown by a comparison of the different types of pneumonia which have been encountered at Camp Upton.

During the period from October 7, 1917, to April 20, 1918, 300 cases of pneumonia were admitted to the Base Hospital at Camp Upton. Of the 300 pneumonias, 283 had careful bacteriological examinations of the sputum; 136, or almost half, were found to be of streptococcus origin, and 137 were caused by pneumococcus. There were 49 cases of streptococcus empyema, showing an incidence of empyema among the streptococcus pneumonia of 36 per cent. On the other hand there were only 15 cases of pneumococcus empyema, or an incidence of empyema among the pneumococcus cases of 11 per cent. Finally, there were 16 cases of sterile empyema about equally divided between streptococcus and pneumococcus pneumonia. Altogether, our records show for this period 80 cases of empyema and these 80 cases form the basis for this study.

Before proceeding to the discussion of empyema proper it might be well to refer briefly to the relationship of measles to this disease. In some of the other camps a large percentage of the empyemas, especially those of streptococcus origin, have developed as a complication of post-measles pneumonia. Such has not been the case at Camp Upton. In the first place a comparatively small

number of our measles cases have developed pneumonia, 30 out of 154 cases, with a mortality list of but 2. Furthermore, only 4 cases of empyema have developed among these 30 pneumonias, and of these only 1 died. By referring to the table, however, it will be seen that a considerable number of the empyemas developed in pneumonias which followed influenza, tonsillitis and other mild infections. We are quite certain, however, that streptococcus empyema may develop from a primary streptococcus pneumonia. Two of the pneumonia cases which followed mumps were complicated by empyema, both of these being streptococcus infections.

In this study special attention had been devoted to the bacteriological examination of the cases. In most instances direct specimens of the patients' exudate were collected as soon as the diagnosis was made and taken to the laboratory at once for examination. The bacteriology of the sputum was carried out as follows: A fresh specimen of sputum thoroughly washed with sterile saline and smears made for the Gram stain. The sputum was then emulsified and $\frac{1}{5}$ c.c. added to a tube of Avery's blood broth, which was then incubated in the water-bath at 37° C. for five hours. At the end of this time smears were made, and if a pure culture was found, agglutination tests were done at once in the usual manner. Under all conditions, however, subcultures were made from broth on plain blood-agar plates and colonies were picked from these on the following day for further study. In many cases the blood broth method was controlled by injections of the sputum into the mouse and identification of the organism was determined from the peritoneal exudate or the hearts. In a few instances cultures of the sputum were made directly on blood-agar plates. The results obtained by the various methods have been surprisingly consistent.

Classification of Empyemas. By referring to the table it will be seen that our 80 cases of empyema naturally fall into three groups: (1) pneumococcus empyemas; (2) streptococcus empyemas; (3) sterile empyemas. These three groups will be discussed separately.

TABLE OF EMPYEMA CASES.

	Name.	Type of pneumonia.	Onset of empyema.	Type of organism. Sputum.	Pleural fluid.	Blood culture.
1.	Lynch, Leo.	Sec. Infl.	4.10 to 4.16	Pn. II	Pn. II	
2.	Ary, Geo.	Primary	1.90 to 1.14	Pn. I	Pn. I	
3.	Breen, James	Sec. infl.	12.15 to 1.1	Pn. I	Pn. I	
4.	O'Toole, A.	Sec. infl.	12.18 to 1.4	Pn. I	Pn I	Neg.
5.	Lewis, L.	Sec. pleur.	3.15 to 3.22	Pn. II	Pn. II	
6.	Smith, Wm.	Primary	3.22	Pn. II	Pn. II	
7.	Parker, B.	.....	2.10 to 2.22	Pn. II	Pn. II	Pn. II
8.	Rhea, J.	Sec. infl.	3.70 to 4.8	Pn. IV	Pn. IV	
8.	McDavid, J.	Primary	3.26 to 3.30	Pn. IV	Pn. IV	
10.	Farley, Chas.	Sec. mitral stenosis	1.40	Pn. IV	Pn. IV	Pn. IV
11.	Becker, J.	Sec. infl.	12.25 to 1.1	Pn. IV	Pn. IV	
12.	Herbert, B.	Sec. bron.	3.18 to 4.2	Pn. IV	Pn. IV	Neg.
13.	Levine, M.	Primary	3.13 to 4.6	Pn. IV	Pn. IV	
14.	Davis, Geo.	.....	.....	Pn. II	Pn. IV	
15.	Mehling, F.	Primary	4.60 to 4.14	....	Pn. IV	
16.	Hatten, Wm.	Primary	2.70 to 2.21	Strep. hem.	Strep. hem.	Neg.
17.	Ryan, Morris	Primary	3.12 to 3.13	Strep. hem.	Strep. hem.	Neg.
18.	Adkins, G.	Primary	3.18 to 3.30	Strep. hem.	Strep. hem.	Neg.
19.	Woolums, L.	Primary	3.30 to 4.4	Strep. hem.	Strep. hem.	
20.	Castle, L.	Primary	3.13 to 4.3	Strep. hem.	Strep. hem.	
21.	Engelkes, F.	Primary	3.30 to 4.1	Strep. hem.	Strep. hem.	
22.	Farmer, L.	Primary	3.12 to 3.21	Strep. hem.	Strep. hem.	
23.	Reynolds, O.	Sec. bron.	3.25 to 3.31	Strep. hem.	Strep. hem.	
24.	Gustal, A.	Primary	4.50 to 4.9	Strep. hem.	Strep. hem.	
25.	Feiertag, H.	Primary	3.29 to 4.2	Strep. hem.	Strep. hem.	Neg.
26.	Laversey, F.	Sec. bron.	3.90 to 3.20	Strep. hem.	Strep. hem.	
27.	Edley, F.	Primary	3.21 to 4.9	Strep. hem.	Strep. hem.	
28.	Green, Delos	Sec. measles	3.26 to 4.3	Strep. hem.	Strep. hem.	
29.	Van Skiver, S.	Sec. bron.	3.16 to 3.17	Strep. hem.	Strep. hem.	
30.	Brickford, C.	Sec. bron., pharyngitis, Ger. measles	1.70 to 1.17	Strep. hem.	Strep. hem.	
31.	Jackson, J.	Primary	3.40 to 3.5	Strep. hem.	Strep. hem.	
32.	Wright, G.	Sec. infl.	3.50 to 3.9	Strep. hem.	Strep. hem.	
33.	Winston, G.	Sec. measles	3.24 to 4.7	Strep. hem.	Strep. hem.	
34.	Thomas, S.	Primary	3.60	Strep. hem.	Strep. hem.	
35.	Watson, J.	Primary	12.25 to 1.6	Strep. hem.	Strep. hem.	
36.	Scott, T.	Primary	3.10 to 3.3	Strep. hem.	Strep. hem.	
37.	McCann, A.	Primary	3.11 to 3.15	Strep. hem.	Strep. hem.	
38.	Gettis, T.	Primary	2.18 to 2.20	Strep. hem.	Strep. hem.	Neg.
39.	Gannon, J.	Sec. infl.	3.70 to 3.10	Strep. hem.	Strep. hem.	St. hem.
40.	Carter, Wm.	Mumps sec.	2.11 to 2.23	Strep. hem.	Strep. hem.	Neg.
41.	Mailler, J.	Sec. infl.	1.28 to 2.11	Strep. hem.	Strep. hem.	Neg.
42.	Cummings, J.	Sec. infl.	3.50 to 3.5	Strep. hem.	Strep. hem.	
43.	Purcell, J.	Primary	2.40 to 2.9	Strep. hem.	Strep. hem.	
44.	Mack, Wm.	Sec. mumps	3.70 to 3.7	Strep. hem.	Strep. hem.	
45.	Jackson, C.	Primary	3.80 to 3.8	Strep. hem.	Strep. hem.	
46.	Jenkins, Wm.	Sec. pharyn.	.....	Strep. hem.	Strep. hem.	
47.	Grace, Geo.	Primary	4.14 to 4.16	Strep. hem.	Strep. hem.	
48.	Bondreau, L.	Sec. Tonsil.	4.50 to 4.6	Strep. hem.	Strep. hem.	
49.	Szymanik, L.	Primary	4.17 to 4.20	Strep. hem.	Strep. hem.	Neg.
50.	Rotach, J.	Primary	4.17 to 4.21	Strep. hem.	Strep. hem.	
51.	Pfaff					
52.	Rivers, H.	Primary	1.10 to 1.20	Strep. virid.	Strep. virid.	
53.	McCauley, Ed.	Primary	3.15	Strep. virid.	Strep. virid.	St. virid.
54.	Feinberg, A.	Primary	1.80 to 1.14	Strep. virid.	Strep. virid.	
55.	Coleman, R.	Primary	1.12 to 1.24	Strep. virid.	Strep. virid.	Neg.
56.	Bennett, A.	Primary	12.15 to 12.26	Pn. 2	Strep. virid.	

TABLE OF EMPYEMA CASES.

	Treatment.	Termination.	Postmortem findings.
1.	Aspiration	Died, Mar. 17, 1918	
2.	Resection	Recovered	
3.	Resection		
4.	Resection	Duty, Feb. 19, 1918	
5.	Resection	Convalescent (?)	
6.	No record	Died, Mar. 26, 1918	Lobar pn. l. u. and l. r. u. emp. lt.
7.	Thoractomy	Duty	
8.	Resection	Prognosis (?)	
9.	No record	Died, Apr. 3, 1918	Lobar pn. rt. bilat. emp. sacc.
10.	No record	Died, Jan. 10, 1918	Lobar pn. L. L. L. and rt. u. emp. lt. veg. endocardit. infarcts in lt. lung.
11.	No record	Duty, Jan. 31, 1918	
12.	Resection	Prognosis (?)	
13.	Resection	Prognosis (?)	
14.	Resection	Convalescent	
15.	Aspiration	Died, Apr. 14, 1918	
16.	Resection	?	
17.	Resection	Died, Mar. 23, 1918	Broncho pn. emp. sacc. rt. abscesses in rt. lung; fibrin. pericarditis.
18.	Operation resection	Convalescent	
19.	Aspiration	Died, Apr. 12, 1918	Broncho pn. emp. rt. sacc.
20.	Resection	Convalescent	
21.	Aspiration	Died, Apr. 2, 1918	Broncho pn. emp. lt. l. L. L. L. acute fibrin. percardit.
22.	Resection	Convalescent	
23.	Resection	Prognosis (?)	
24.	Aspiration	Died, Apr. 10, 1918	Broncho pn. lt. emp. lt. fibrinous percardit.
25.	No record	Died, Apr. 3, 1918	Broncho pn. (interst.) emp. lt.
26.	Resection	Convalescent	
27.	Resection	Convalescent	
28.	Aspiration	Died, Apr. 11, 1918	Pn. rt. lobe. emp. rt. sacc. emp. lt.
29.	Resection	Died, Mar. 18, 1918	
30.	Resection	Convalescent	
31.	Resection	Died, Mar. 5, 1918	
32.	Resection	Died, Mar. 10, 1918	
33.	Resection	Convalescent.	
34.	No record	Died, Mar. 8, 1918	Lobar pn. L. L. L. emp. lt. mult. abscesses of lt. lung.
35.	Aspiration	Died, Jan. 17, 1918	Broncho pn. lt. (interst.) emp. lt. fibrino-pur. pericardit.
36.	Resection	Died, Mar. 3, 1918	Lobar pn. R. L. L. abscess of lung. Emp. rt.
37.	Resection	Died, Mar. 19, 1918	
38.	Resection	Died, Mar. 27, 1918	Lobar pn. L. L. L. emp. lt. pneumothorax lt. infarct. of spleen.
39.	Resection	Convalescent	
40.	Resection	Recovered	
41.	Resection	Died, Feb. 24, 1918	Broncho pn. R. L. L. lobar pn. L. U. L. emp. rt.
42.	Resection	Died, Mar. 11, 1918	
43.	Resection	Died, Mar. 12, 1918	Broncho pn. rt. lung (interst.) type, fibrino-purl. pericardit. emp. rt.
44.	Resection	Died, Mar. 9, 1918	Lobar pn. R. L. L. emp. rt. sacc. fibrino-pur. pericardit.
45.	Resection	Died, Mar. 10, 1918	Broncho pn. bilat., emp. bilat. sacc.
46.	....	Died	Sarcoma testes and lung broncho pn. emp. lt., acute gen'l. peritonitis.
47.	Aspiration		
48.	....	?	Broncho pn. (bilat.) emp. lt. sacc. fibrinous pericarditis.
49.	Aspiration	Died, Apr. 21, 1918	
50.	No record	?	
51.	Resection	Convalescent	
52.	Incision	? Duty	
53.	No record	Died, Mar. 30, 1918	Broncho pn. rt. lung, lobar pn. L. L. L. emp. lt. sacc., acute strept. meningit.
54.	No record	Died, Jan. 14, 1918	Broncho pn. (interst.) rt. L. L. emp. rt. sacc. fibrino-pur. pericardit.
55.	No record	Died, Feb. 3, 1918	Broncho pn. (interst.) emp. rt. sacc. fibrino-pur. pericarditis.
56.	No record	Died, Dec. 29, 1917	Broncho pn. bilat. (interst.) emp. lt. mult. abscesses of lungs.

TABLE OF EMPYEMA CASES.

Name.	Type of pneumonia.	Onset of empyema.	Type of organism. Sputum.	Pleural fluid.	Blood culture.
57. Frick, A.	Sec. infl.	1.23	Pn. −2	Strep. hem.	
58. McHale, P.	Sec. infl.	1.30 to 2.14	Pn. −2	Strep. hem.	
59. Costella, J.	Sec. tonsil. bronch?	1.21 to 2.17	Pn. −3	Strep. hem.	
60. Mulqueen, G.	Sec. infl. pharyng.	1.18 to 1.26	Pn. −4	Strep. hem.	
61. Purnhagen, A.	Primary	12.22 to 1.20	Pn. −4	Staph. aureus	Neg.
62. Lantry, J.	Sec. bron.	12.21 to 12.29	Pn. −4	Strep. virid.	
63. Conniers, N.	Primary	1.22 to 2.18	Pn. −4	Strep. hem.	Neg.
64. Jones, Wm.	Primary	3.40	Pn. −4	Strep. hem.	Neg.
65. Davis, D.	Sec. mumps	1.26 to 2.19	Pn. −4	Strep. hem.	
66. Glover, Geo.	Sec. measles	12.60 to 1.27	Pn. −1	Sterile	
67. Stenzel, W. R.	Sec. infl.	3.27 to 3.30	Pn. −1	Sterile	
68. Thomas, J.	Sec. pleur.	2.60 to 2.20	Pn. −2	Sterile	Neg.
69. Carter, T.	Primary	2.26	Pn. −2	Sterile	Neg.
70. Moore, Ed.	Sec. measles	12.18 to 1.3	Pn 3	Sterile	Neg.
71. Earl Starns	Primary	1.30 to 2.25	Pn. −4	Sterile	
72. Callan, A	Primary	3.30 to 4.9	Pn. −4	Sterile	
73. Teets, A.	Primary	1.30 to 1.25	Pn. −4	Sterile	
74. Harding, F.	Sec. broncho.	3.70 to 3.11	Pn. −4	Sterile	
75. Turner, T.	Primary	3.21 to 3.23	Pn. −4	Sterile	
76. Moore, Theo.	Sec. broncho.	3.11	Strep. hem.	Sterile	
77. Vicker, O.	Primary	4.80 to 4.15	Strep. hem.	Sterile	
78. Masterbrook	Sec. scarlet fever	3.30	Strep. hem.	Sterile	
79. Clarence, R.	Sec. broncho.	1.70 to 1.14	Strep. virid.	Sterile	
80. Scott, D.	Sec. infl.	3.12 to 3.17	Strep. virid.	Sterile	Neg.

1. *Pneumococcus Empyemas.* In the present series of 80 cases there were only 15 that showed the pneumococcus from culture of the pleural exudate. These pneumococcus empyemas differed in no essential respect from those seen in civil practice. Without exception they developed in cases of lobar pneumonia in which the pneumococcus had been previously isolated from the sputum. This type of empyema usually develops late in the course of the disease when a patient is convalescent. There is a sudden rise in temperature and a corresponding increase in pulse-rate. The patient, however, may not be very ill. Frank signs of fluid are usually present, and upon exploring the chest over this area cloudy or creamy pus is withdrawn which, on examination, shows many pus cells and capsulated pneumococci.

Pneumococci of Types I, II and IV are all represented in this group, and in all except one case the same kind of pneumococcus was found in both sputum and pleural exudate. In this case pneumococcus Type II atypical was isolated from the sputum and pneumococcus Type IV from the pleural fluid. Of this group of 15 cases 5 died, a mortality of 33 per cent. One case developed

TABLE OF EMPYEMA CASES.

	Treatment.	Termination.	Postmortem findings.
57.	No record	Died, Feb. 11, 1918	
58.	Resection	Prognosis (?)	
59.	Resection	Recovered	
60.	Resection	Died, Jan. 28, 1918	
61.	Resection	Died, Feb. 11, 1918	
62.	No record	Died, Dec. 21, 1917	Broncho pn. (interst.) emp. sacc. rt. fibrino-pur. pericarditis, mult. abscesses of right lung.
63.	Resection	Convalescent.	
64.	Resection	Died, Mar. 13, 1918	Lobar pn. lt. lung and rt. L. L. Emp. right.
65.	Resection	Convalescent	
66.	Resection	? Convalescent	
67.	Aspiration	Died, Apr. 1, 1918	
68.	Resection	Died, Mar. 15, 1918	
69.	No record	Died, Mar. 3, 1918	
70.	Resection	Died, Mar. 5, 1918	Gen'l military T. B. pn. lt. lung, emp. left.
71.	No record	Duty, Apr. 7, 1918	
72.	No record	?	
73.	Resection	Died, Jan. 21, 1918	
74.	Aspiration	Duty	
75.	Aspiration	Convalescent	
76.	No record	Died, Apr. 19, 1918	
77.	No record	Convalescent	
78.	No record		
79.	Resection	Died, Mar. 3, 1918	
80.	Resection	Duty, Apr. 22, 1918	

a pneumococcus endocarditis and septicemia. One of the Type II cases on blood culture showed twenty-four colonies per 1 c.c. of blood, but made an excellent recovery after rib resection and drainage. This case showed a curious metastatic focus—a perithyroid abscess. The fatal cases of this group all died early in the disease apparently from the intensity and extent of the pneumonia rather than from the concomitant empyema.

2. *Streptococcus Empyema.* By far the largest number of our empyema cases were streptococcus infections and it is this group that constitutes the most interesting phase of the problem. For convenience of discussion it will be well to subdivide this group into three subgroups.

(*a*) Streptococcus hemolyticus empyemas.

(*b*) Streptococcus viridans empyemas.

(*c*) Streptococcus empyemas following pneumococcus pneumonia.

(*a*) *Streptococcus Hemolyticus Empyemas.* In this group there were 29 cases in which Streptococcus hemolyticus was recovered in pure culture from the empyema fluid and in which bacteriological examination of the sputum showed the same organism.

CLASSIFICATION OF EIGHTY EMPYEMAS

I. Pneumococcus in both sputum and pleural exudate.

	Cases.	Deaths.
Type I in both	3	0
" II "	4	2
" IV "	6	2
" II in sput. type IV in pl. ex.	1	0
Sput. not examined type IV pl. ex.	1 (?)	1
	15	5 (33%)

II. Streptococcus in both sputum and pleural exudate.

	Cases.	Deaths.
Strept. hemol. in both	29	16
Sput. not examined st. hem. in pl. ex.	7 (?)	6
Strep. virid. in both	4	3
	40	25 (60%)

III. Mixed Infections.

	Cases.	Deaths.
Pn. type II in sputum; Strep. vir. in pl. ex.	1	1
" II " " hem. "	2	1
" III " " " "	1	0
" IV " " " "	4	2
" IV " " vir. "	1	1
" IV " Staph. aur. "	1	1
	10	6 (60%)

IV. Sterile Empyemas.

	Cases.	Deaths.
Pn. type I sputum	2	1
" II "	2	2
" III "	1	1
" IV "	5	1
Strept. hemolyticus	3	1
" viridans	2	1
	15	7 (50%)

There were 7 other cases in which the Streptococcus hemolyticus was recovered from the pleural exudate, but in which for some unavoidable reason the sputum was not examined. In these 7 cases, however, the clinical course and physical signs strongly indicated a streptococcus pneumonia, so they probably belong to this group. These 36 cases constitute a fairly definite and characteristic picture. The patient who often gives a history of some recent infection of the upper respiratory tract is admitted to the hospital

complaining of a cough, fever and occasionally pain in the side. The onset, as a rule, is gradual, though it may be very sudden. Many cases are admitted with a diagnosis of influenza or bronchitis. The cough is usually dry in character and is often entirely absent, a feature which makes it difficult or impossible to collect a satisfactory specimen of sputum. The sputum itself is rather characteristic. It is usually of a white or yellowish color, quite viscid and mucopurulent. The rusty or hemorrhagic sputum of lobar pneumonia is rarely seen. The fever usually runs an irregular course, and considerable febrile periods, succeeded by rapid oscillations, as in an active sepsis, appear at the onset. The pulse is comparatively slow in this early stage of the pneumonia, but is consistently in proportion to the temperature. The respiratory rate is, however, proportionately high throughout. Pain in the side is a very inconstant symptom, and when present is an additional cause of the inspiratory distress. Inspiratory pain is not usually long continued, and few cases have required strapping or opiates because of it.

1. *Physical Signs before Onset of Empyema.* The physical signs before the onset of empyema are often indefinite. On percussion, areas of dulness may or may not be present at first. Moist crackling rales are nearly always to be heard, at times confused with the pleuritic friction rub, but typical bronchial voice and breathing are rather unusual signs at the onset of the pneumonia. More often the voice and breath sounds are faint. Furthermore, one must say that there are few distinctive signs or symptoms at the onset of the pneumonia, which serve to differentiate cases which subsequently develop empyema from those that do not.

2. *Physical Signs after Onset of Empyema.* In several instances cases have entered the hospital under the regimental diagnosis of empyema; careful investigation of the history has, however, in all these shown a story of several days of indisposition and probable fever. Cases which have, however, entered the hospital, usually because of prostration and a slight febricula and before any physical signs indicative of either pneumonia or empyema appeared, have often developed under observation surprisingly early empyemas. Thus our group of streptococcus cases has shown a positive

diagnosis of empyema possible in an average of 5.4 days after admission. Which one takes into consideration the fact that 3 of these cases developed their pneumonia in the hospital as a secondary process two or three weeks after admission, the very early onset of streptococcus empyema is impressively demonstrated. Suffice it then to conclude that this empyema develops with surprising rapidity and often before a conclusive diagnosis of pneumonia, in addition to pleurisy, could be made, except by the assistance of the *x*-rays. It is therefore seen that these empyemas are imposed upon and do not merely succeed the active stages of pneumonia. The prognostic significance of this fact must be apparent to all.

In our early experience with the disease in three instances we were surprised to find empyema at postmortem where simple lobar pneumonia had been expected. In 2 of these instances the physical signs should certainly have given the diagnosis, and mere indolence on the part of the ward surgeon accounted for this failure. Careful analysis of the charts in these 3 cases, however, presented nothing of a symptomatic character which would lead anyone unsophisticated in this epidemic to suspect the development of an empyema, for the picture was typically and solely that of an pneumonia. Nor was this finding limited to our early cases alone, for not seldom, but very frequently, even after we were keenly alive to the frequency of empyema the needle and the *x*-rays have detected rapidly developing empyemas which were entirely unmarked by alterations in the clinical picture and with strikingly few modifications in the physical signs.

One of the most constant and suggestive signs has been the appearance of profuse sweats comparable in degree and in exhaustion to those of acute rheumatic fever. The entire surface of the body, more notably the head and the neck, are frequently beaded with large drops of sweat. These signs are unaccompanied by chills, which is found to be a rather unusual symptom at any stage of these cases and one which never appears but at the period of onset. Under onset we have mentioned the marked exhaustion which typifies these cases. This, however, is in no way characteristic of the empyema, since it may be also strikingly manifest

in the simple streptococcus pneumonia. It is usually more pronounced when a purulent exudate is forming or has formed than when the pneumonia is complicated. When the exhaustion is very striking we have learned to be very constantly on guard and to apply the needle with even more diligence than ordinary, though not infrequently with negative results. Acceleration of the respiration is another suggestive sign, though of course in recognized pneumonia it can be considered as the only relative value; but there can be no doubt that as the pus begins to form there is a very perceptible increase in the respiratory rate above that which may be attributed to the pneumonia alone, and with increase in rate is also to be found increased dyspnea and respiratory distress. There is nothing characteristic in the temperature and pulse curves in the early stages that suggest the onset of empyema. Of course, when it develops later in the pneumonia when pulse-rate and temperature are falling an ascent in both appears. It rarely assumes a septic form, however.

In ordinary pleurisy, and particularly in a process which so largely, as in these cases, involves the bases and diaphragmatic pleura, one is accustomed to consider abdominal rigidity a sign of considerable value, especially when, as is usually the case in this epidemic, it is monolateral at the onset. This sign or picture has been strikingly absent in the cases which we present in this study. In but 4 of the cases do we recall this indication as demonstrable. It was often entirely absent even in instances in which we were able to demonstrate readily the fact that the diaphragmatic pleura was involved. Head zones of hyperesthesia is another frequent sign that one finds in cases of pleurisy of whatever origin but which has been strikingly absent in our cases. Another negative sign which has impressed us very much has been the very general absence of or diminution in degree of the stabbing pain which is so generally complained of in the onset of pleurisy. This has not been frequent in our cases even when the onset of pleural effusion seemed to take place synchronously with or but slightly later than the first pneumonic symptoms or signs. On the contrary we have all been impressed with frequency with which skin tenderness, not hyperesthesic, has been evident on even ordi-

narily vigorous percussion over the involved area. Not seldom this tenderness, which is a deep and not a superficial one, has largely determined us in selecting a point for needling.

Our study of the physical signs in general as regards this group of unusual cases has been disappointing and often most difficult of explanation. As a result of great disparity between positive physical signs and lesions our ward surgeons have been instructed to needle or fluoroscope even when all signs point away from the existence of pleural effusion. We both feel that we have unlearned far more physical signs of pleural fluid than we have perfected. All observers have been struck with the great frequency of skodaic resonance, and many times it has been most typical over areas from which the needle gave abundant fluid. Postmortem and *x*-ray study of this sign has taught us to consider it as due in many instances to early pulmonary compression of more than the usual degree, because of the fact that the pleura in these cases was but little thickened and the adjacent pulmonary tissue but little involved by consolidation. That this sign may be transmitted through a considerable amount of superadjacent fluid has been demonstrated to us numerous times and over areas where no transmission of abdominal tympany could be assumed. Probably, for the same reason, breath-sounds, vocal and tactile fremitus, have been transmitted through massive exudates with great and deceptive distinctness. We have been forced to exaggerate alterations in these signs or to totally ignore their significance. Doubtless the more limpid and less cell concentration of the fluid present in these cases as compared to that of the antebellum conception of empyema has also something to do with the much modified physical signs. Beyond question the single physical sign which we come to consider as of most absolute value in the detection of these effusions is alteration in percussion. A high-pitched note or the flattening of the customary resonance is a sufficient indication for a tap in these cases, and if the tap be a dry one a repetition is justified.

In six instances distinct and unmistakable pneumothorax has developed before the cases have been tapped, and in quite frequent instances minor degrees of this phenomenon appeared. In none

of them could the usual explanatory causes be found present. There had been no possible injury to the thorax, no bacteria causing gas formation were found in the fluid and no possible cause of pulmonary laceration could be made out clinically or in the 3 instances that came to autopsy. The amphoric splash and metallic tinkle of mingled fluid and air has come and gone in several typical cases also without a reasonable explanation. One hypothesis for these curious and surprisingly early manifestations is that they may be due to rupture of minute pulmonary abscesses which thus allow the escape of air into the pleural cavity. Microscopic study lends some support to this theory.

In a discussion of the pathological anatomy of the disease, mention will be made of the frequent development of pleuropericarditis, and the very early appearance of this lesion is quite as remarkable as the appearance of the empyema itself. Usually when this process is present it becomes very early apparent from a primary pleuropericardial friction rub which is commonly so distinct as to become unmistakable; it diminishes, of course, as the effusion develops. As a natural sequence of this complication a pure pericarditis appears also with considerable frequency. Postmortem evidence, as will be stated also under the pathological anatomy, shows that this first involves the parietal layer of the chamber, the visceral layer of the membrane only becoming involved later. Under our intensive method of study of the cases the complication has only rarely escaped detection clinically. The amount of fluid which may thus accumulate in the sac may be very large, as much as 900 c.c. for example. The character of this fluid is precisely like that seen in the pleural cavities. First it has a typical clear to turbid urine appearance, later on it becomes highly fibrinous with the characteristic deposit of fibrin on both layers of the membrane and the ultimate transformation into pus of a clinical type. The bacteriology of the pericardial exudate is precisely like that of the pleural fluid. In one case we have been able to isolate the pneumococcus, but even in demonstrated instances of pneumococcus infections it has usually been a streptococcus.

There are no signs or symptoms that appear in the pericardial

complication which differ from those customarily seen in this condition. In 2 instances the pericardial sac was drained, 1 early in the course of the complication and 1 late after the fluid had become thick and gelatinous pus. Both recovered.

Studies of the total and differential white cell has been very disappointing as a diagnostic measure. With the acknowledged existence of the pneumonia there is nothing shown suggestive of a developing exudate, nor of the fact that this fluid is of a highly septic character.

The blood-pressure is that usually seen in pneumonias. Of course, in fatal cases the pulse pressure becomes very much diminished as *exitus* approaches, and with it the usual tachycardia and cardiac arrhythmias which are common to the just premortem status.

The urine provides no data of an unusual character and nothing of a diagnostic value.

The *x*-rays have been used in almost all cases in diagnosis, not so frequently for the demonstration of fluid as to indicate the extent and nature of the pulmonary process. In most cases, so far as the demonstration of empyema is concerned, the *x*-rays, particularly stereoscopic plates, have been most useful. It is much more necessary for the location of pulmonary disease. In several instances it has been misleading, indicating no fluid in which the needle showed it to be present, and less frequently the opposite fault has been found. The fluoroscope has not always been employed as a diagnostic routine, for the reason that most of our cases have been so gravely ill that they could not be set up, and it was soon found that satisfactory plates could only be obtained when the patient was raised up on a rack and kept in this position for a short period of time until gravity had caused the fluid to occupy a pendent part of the thorax, when only it became demonstrable in certain cases. For a most satisfactory method of accomplishing this we are much indebted to our colleagues at Camp Devens, who first demonstrated their excellent practice to us. Our experience has shown us, however, that one may not depend absolutely upon the *x*-rays in diagnosis of empyema. In several instances it has misled us, particularly when the fluid was encap-

sulated at the left internal and posterior angle of the thorax and its shadow obscured by that of the heart. The use of the *x*-rays is about indispensable in these cases, but it will not alone keep the lazy clinician out of trouble with the pathologist.

Frequent needlings have been most certain and more satisfactory in our hands. When the puncture was to be made for diagnosis only a fine hypodermic needle from 3 or 4 cm. in length attached to an ordinary 4 c.c. Luer syringe is used. The fluid in most questionable instances is so limpid that it can be very readily obtained in this manner in quite sufficient quantity for bacterial and histological diagnosis, and the pain caused by this needling is so slight that the patients do not object to very frequent taps that we often find necessary. We ordinarily do our aspirations with the Potain aspirator, but sometimes when the amount to be aspirated is small an ordinary 20 c.c. syringe (glass) is used. We cannot commend the use of the needle too highly; we find it indispensable in diagnosis.

Character of the Empyema Fluid. The pleural exudate when removed is usually light yellow, often with a greenish tinge, and in the early stages only slightly cloudy. Later in the disease it may take on a distinctly purulent character. Smears from the fluid show pus cells in large numbers and large round or slightly flattened cocci arranged in short chains of two to ten organisms. We have observed that the bacteria are much more numerous in the streptococcic empyema than in the pneumococcic empyemas. Cultures from the exudate on blood-agar plates show after twenty-four hours' incubation many small, elevated, opaque colonies of a pearl gray color, each surrounded by a sharply defined zone of hemolysis. Subcultures in blood broth produce diffuse clouding of the media, with a heavy sediment in the bottom of the tube. Rapid destruction of the blood cells takes place and the blood broth takes on a brilliant claret red color. Smears from the blood broth show chains of cocci similar in all respects to all seen in the smears from the pleural exudate.

The mortality rate in this group was very high, our experience in this respect corresponding to that met by clinicians in other camps. Of the 36 cases, 22 died, a mortality rate of 61 per cent.

(*b*) *Streptococcus Viridans Empyemas.* In this group of cases cultures from both the sputum and the pleural exudate showed a streptococcus of the non-hemolizing variety. There were 4 cases of this type. Clinically these cases have differed in no respect from the Streptococcus hemolyticus cases. All 4 of these were cases of bronchial pneumonia and the symptoms and signs of empyema were similar in every way to those of Streptococcus hemolyticus empyema. Three out of the 4 cases died.

(*c*) *Streptococcus Empyemas following Pneumococcus Pneumonias.* This very interesting group of mixed infections consists of 9 cases and corroborates the findings of Cole and McCallum at Fort Sam Huston. In these cases the pneumococcus was cultivated from the sputum, but cultures from the pleural exudate gave either Streptococcus hemolyticus or viridans. Pneumococci of Types II, III and IV are represented in this group of mixed infections. There is also a case which we include in this group which gave pneumococcus Type IV in the sputum but Staphylococcus aureus in the exudate. It is possible, however, that in this case the staphylococcus infection developed after operation and drainage had been performed. The majority of these cases were frank lobar pneumonias. There were 2 cases diagnosed as broncho-pneumonia, but it may have been that in these 2 cases mouth pneumococci confused the bacteriological picture. This was also a highly fatal group, 6 out of 10 cases dying. Clinically the empyema in this group possessed all the characteristics of the pure streptococcus type.

Summarizing these three subgroups there were 49 streptococcus empyemas with 30 deaths, a mortality rate of 61 per cent.

3. *Sterile Empyemas.* In addition to the 65 empyemas already mentioned we have included in our study 15 cases in which fluid of a purulent or semipurulent nature was removed from the pleural cavity, but from which cultures were sterile. In several of these cases Gram-positive cocci were seen in smears from the fluid. They usually showed, however, some sign of disintegration and could not be cultivated even on blood media. Ten of these empyemas were associated with pneumococcus pneumonias of the lobar type and 5 died. Five cases were associated with streptococcus pneumonia and 2 of these died.

Blood Cultures. Blood cultures were done on 20 of our empyema cases, with only 3 positive results, 2 of these were pneumococcus cases and 1 Streptococcus hemolyticus. In the early part of the year, blood cultures were taken on every case of pneumonia, but when it was found that the results were almost universally negative this procedure was discontinued as a part of the routine examination. The clinical picture might lead one to suspect that this disease was one phase of a general septicemia. The character of the temperature curve, the pulse-rate, the profound prostration, the rapid course of the disease and the high mortality all support this impression. The rare occurrence, however, of metastatic foci points strongly against this theory. Strangely enough, 2 out of the 3 cases in which the blood culture was positive made uneventful recoveries.

Pathogenesis of Empyema. All of our cases of empyema have been associated with pneumonia, but in many of the streptococcus cases the pneumonic process has been relatively slight, as verified by physical signs, *x*-rays and autopsies. Cases of Streptococcus hemolyticus empyema have been reported from other camps in which no evidence of concomitant pneumonia could be obtained, and such a phenomena seems reasonable in consideration of our own experience. It is quite certain that in many cases the empyema has far outweighed the pneumonia in clinical importance. It is probable, however, that in the majority of cases streptococcus empyema develops from a bronchopneumonia, the infectious organism being conveyed to the pleura either by the way of the lymphatics or by the direct extension of one of the small abscesses so frequently seen through the pleural coat. The severity of the pneumonia may be a factor in the development of the empyema, but this is a difficult point to settle, since the onset of the empyema early in the course of the disease masks the real character of the pulmonary condition. It may be stated, however, that streptococcus empyema has usually appeared in those cases of pneumonia that have seemed to be severe infections.

The question of ward infections occur in this disease, that is, if patients suffering from pneumonia of whatever type are likely to contract a streptococcus empyema from their associates in the

ward or from streptococcus carriers, receives some confirmatory evidence from the fact that our group of cases includes 10 instances in which a pneumococcus infection of the lung was associated with a streptococcus empyema.

On the other hand, we have seen nothing clinically that would seem to substantiate this hypothesis, and since we have adopted careful methods of isolation of cases in the wards by means of screens and punctitious gowning, capping and veiling of attendants, nurses, physicians and convalescent patients no change in incidence has been evident. We must note, however, that our camp was entirely free from streptococcus empyema and we were somewhat skeptical as to its nature until we received a large contingent of colored troops from another encampment said to have suffered much from this condition. The complication is no longer limited to ultrabrunettes with us at Upton.

The likelihood of an autogenous infection from streptococci already in the mucous tract of patients before they contract the pneumonia seems to us a much more probable factor. This has received some quite suggestive corroboration at Camp Upton, from a series of cultures made during an epidemic of streptococcus pharyngitis, in the convalescence of which a considerable number of pneumonias developed. Cases of pneumonia followed by empyema and all apparently inaugurated by a preliminary pharyngitis are found on our lists. In several probable instances this matter has not been followed with sufficient accuracy to justify more than a reasonable suspicion.

Pathology. Altogether, 27 of the empyema cases came to autopsy. Three of these were pneumococcus empyemas, 1 gave sterile cultures and the remaining 23 all showed streptococci in smears and cultures.

The 3 pneumococcus cases were associated with typical lobar pneumonia, with consolidation in the side involved. The fluid in all 3 of these cases was frankly purulent, and in 1 case there were pockets of pus between the lobes of the lung. One case was associated with acute vegetative endocarditis of pneumococcus origin. In all 3 cases the pleura was covered with a thick layer of fibrin, which could be readily removed from the underlying membrane.

The 1 postmortem case of empyema from which cultures during life had been sterile showed at autopsy pulmonary tuberculosis and tuberculous pleuritis.

The remaining group of 23 cases all showed streptococci in the pleural exudate. Three of these cases (Lantry, Jones and Bennett) belonged to the mixed group of infections. They had been classified from sputum examination as pneumococcus infection of the lungs. The cultures from the pleural exudate gave in 2 cases a non-hemolyzing type of streptococcus and 1 case the hemolytic streptococcus. At autopsy all showed typical lobar pneumonia, but in addition patches of bronchopneumonia were present in those portions not involved in the lobar process. In 3 other cases bacteriological examination of both sputum and pleural exudate gave the non-hemolyzing or green streptococcus. All 3 of these cases showed a patchy type of consolidation and were classed as bronchopneumonias. The empyema in this group was of the sacculated type and the fluid was cloudy, yellow and full of flecks of fibrin. In 2 cases which showed purulent pericarditis the process was apparently an extension by direct contiguity from pleura to pericardium, for the pleura adjacent to the pericardium was extensively involved.

The third subgroup in this division is that in which the process in the lungs and the pleura was all of Streptococcus hemolyticus origin. There were 17 of these cases that came to autopsy. Eleven were diagnosed as bronchopneumonia and 6 as lobar pneumonia. The empyema in this group was described as sacculated in half the cases, in the other cases the fluid was lying free in the pleural cavity. The fluid was sometimes cloudy and amber colored, and sometimes distinctly purulent. In the former group there were often a number of large entirely separate pockets which did not communicate with one another. One such pocket was frequently found between the pericardial sac and the anterior flap of the left lung, which lies over it. This probably accounted for the frequency of pericarditis in this group.

The lung on the affected side, wide in these cases, is covered with a fibrinous coat which varies in thickness with the age of the empyema. It is closely adherent to the pleura. The lungs in these

streptococcus cases have nearly all shown the changes described by Cole and McCallum as interstitial bronchial pneumonia. The lung is atelectatic, due to the compression caused by the fluid. On section the bronchioles stand out with remarkable distinctness and are usually filled with pus. The walls of the bronchioles appear thicker than normal and there is an overgrowth of fibrinous tissue throughout the organ which accentuates the fibrous trabeculæ. The thickening about the bronchioles may be so marked as to give them the appearance of small tubercles or miliary abscesses. Even in those cases in which a part or all of a lobe is consolidated, these changes have been observed in other parts of the lung.

Microscopic sections of the lungs in these cases show areas of bronchopneumonia around the bronchioles and an extensive infiltration of small round cells about the bronchioles and bloodvessels. There is a marked tendency toward organization of the exudate in the alveoli which consists of unusually dense fibrin, lymphocytes and desquamated epithelia.

The pleural covering has been converted into a thick coat of granulation tissue, on the surface of which there is a positive layer of fibrin and leukocytes. Small miliary abscesses have been observed in cases sometimes occupying the site of a bronchiole and at other times situated so as to displace a number of the alveoli. In one case these minute abscesses were located about the small bloodvessels.

Other Pathological Conditions Associated with Empyema. The only other pathological condition which occurs in any frequency was suppurative pericarditis. This was found altogether in 9 cases, 8 of which were in the streptococcus series and one in the cases of mixed infections. In one other case a fibrinous pericarditis was found, and in this later case it was easy to understand why the pericarditis accompanies the empyema so frequently. That portion of the parietal pericardium which lay in immediate contact with the left pleura was intensely reddened and covered with a fresh deposit of fibrin. The infection had apparently extended into the pericardium by direct contiguity, probably by way of the lymphatics. In quite a number of these infections of the peri-

cardium a pocket of pus was found between the pericardial sac and the adjacent portion of the left lung.

Abscess of the lung was the next most common pathological finding, and was noted in 5 cases. These abscesses were usually small and multiple, but in 1 case there was a single large abscess located in the center of the consolidated area.

Infarcts were found in 2 cases, 1 in a pneumococcus empyema and 1 in a Streptococcus hemolyticus case.

Acute vegetative endocarditis was noted in 1 of the pneumococcus cases while acute general peritonitis and acute suppurative meningitis were each observed once, and each in connection with a streptococcus infection.

Bilateral empyema was noted in only 2 cases, 1 in a pneumococcus case and 1 in a streptococcus case.

It will be seen from this *resumé* that in spite of the virulence of this infection it was usually confined to the lungs and pleura, with occasional involvement of the pericardium. This would seem to indicate, as already noted, that the disease is not essentially a septicemia.

Unfortunately, microscopic sections have not yet been cut from all these cases, but it seems probable in the light of our past experiences that some or all of these lobar cases will prove on microscopic examination to be the so-called lobar type of bronchopneumonia, or, in other words, a bronchopneumonia in which the patches are so closely packed together as to simulate a true lobar pneumonia.

Treatment. It has not been our original intention to attempt to consider this phase of the subject extensively in this paper. Perhaps our mortality rate in the streptococcus pneumonias should suffice as an excuse for this reticence on our part in this particular, but we do feel it necessary to at least outline what in our experience should not be done in the hope that it may be of assistance to others who are dealing with these same problems. At the onset we feel ourselves forced to say that the unfortunate interposition of lay military commanders and the stoppage of autopsies must be held responsible for further failures in treatment and the much longer and costly method of forcing us to solve this insistent problem by experiment rather than from the basis of more exact

knowledge which the postmortem alone gives to serious inquiring clinicians.

It is, of course, obvious that since most cases of streptococcus empyema develop very early in the course of pneumonia, it cannot do in case operative measures are decided upon to use general anesthetics at random in still active cases of pneumonia, nor does it seem wise to trust the after-treatment of such operative yet acutely medical cases to surgeons alone. Either an entire coöperation must exist between these two departments or the cases, even though operated upon, should be still considered as properly under medical charge.

In ordinary empyema of pneumococcus type we think that there can be but little question that in the larger number of cases diagnosis should be followed by early operation. This older idea has but been confirmed in our minds by such cases of this class as have occurred in this epidemic. As in the usual run of cases operation has in most instances been followed by prompt benefit and reasonably early recovery. The results have been decidedly different in our cases of streptococcus empyema as also in those so-called sterile empyemas which we believe are likewise of streptococcic origin.

Eleven of our 22 mortality list in the Streptococcus hemolyticus group have been operated upon, most of them in the relatively early stages of the empyema, and of the 15 cases which have recovered or are still in the hospital but 8 had a resection done. Study of this recovery list, however, has apparently shown that those cases operated early have almost without fail died, while those in which the operation has been postponed until the pus became thick and gelatinous, frequent aspirations in the meantime having been done, recovered.

As a result of our study of this group we have naturally arrived at the practice of withholding our cases from the surgeon until later in the course of the disease, when the pus had become thick with fibrin and cells.

We have felt that our better success since this method had been adopted has depended in part on the fact that when the pleural cavities are drained through the active stage of the pneu-

monia the rapid collapse of the diseased lung on the operated side has thrown an added strain on the unprepared heart which has been a dominant factor in the cause of postoperative death. Furthermore, when the waiting policy is pursued, not only may the pneumonia improve and the heart adjust itself to the strain thrown upon it, but it has been our observation that the pleura becomes so thickened as a result of the exudate that the subsequent collapse of the lung following thoracotomy is less marked both in degree and in result.

We may summarize our present procedure briefly as follows, but while our results are now better than formerly, we at the same time acknowledge that they are very far from satisfactory.

The case is carried as an ordinary case of pneumonia. As soon as the fluid is discovered and with the insistent use of the needle and *x*-ray this is usually very early determined, the aspirated diagnostic specimen is examined by smear and culture. If the exudate is clear and not turbid nor highly cellular, notwithstanding the presence of the streptococci, it is allowed to remain until it is apparent that it is embarrassing respiration, in which case it is aspirated by Potain. This aspiration is repeated as frequently as seems indicated, careful watch is maintained on alterations in the character of the fluid, and when it becomes thick and viscid the case is deemed to have reached the stage for surgical intervention.

Meantime, of course, the general symptomatic treatment of pneumonia has been followed. As a rule, digitalis is given freely in the early stages, and camphor, adrenalin, caffein, etc., are given as symptomatically indicated. The usual attention is given to elimination, to abundant aëration, and suitable cases are placed out of doors exposed to the sun and air. Temperature is controlled at least in part by hydrotherapy and aërotherapy, and when much pain is suffered or when the patient coughs incessantly or becomes excitable, codein or morphin are used as seems to be indicated.

We are most anxious to attempt prevention and treatment of these cases perhaps by the use of protective sera elaborated from organisms found in our Upton epidemic, and steps in this direction

are now being taken. We feel that until some protective mechanism is discovered that we shall continue to find these cases most unfortunate problems in military medicine.

A marked improvement in results has followed the surgical treatment of these cases of hemolytic empyema since they have been placed exclusively under the care of a single surgeon (Capt. Perry), who has made a special study of this condition, and particularly of its surgical management.

SUMMARY. A highly virulent type of empyema has been prevalent at Camp Upton during the winter and spring months of 1918.

Eighty cases have been observed in a series of 300 pneumonias. Fifteen of these were caused by the pneumococcus and 15 others were sterile; the remainder of the cases were caused by a streptococcus, usually of the hemolytic type.

In this series of cases empyema has been constantly associated with pneumonia of either the broncho or lobar type. Usually a bronchopneumonia has accompanied a streptococcus empyema and a lobar pneumonia the pneumococcus empyemas.

In the great majority of cases the organism which has been found to be the causative agent in the pneumonia has also been isolated in pure culture from the pleural exudate. In 9 cases, however, a pneumococcus pneumonia was associated with a streptococcus empyema.

The onset of the pneumonia and the empyema is apparently simultaneous in many cases.

This epidemic of empyema has been independent of measles and other similar infections.

The clinical symptoms and the physical signs differ from those in classic empyema.

Diagnosis is frequently difficult by reason of the equivocal physical signs and the indefinite symptomatic picture. Diagnostic aspirations are the most certain means of discovery of the condition in its early stage. The *x*-rays stand second in diagnostic importance. Of the physical signs, alterations in percussion seem to be the most helpful.

The interstitial bronchopneumonia recently described by Cole

and McCallum is usually found associated with the streptococcus empyema.

Fibrinopurulent pericarditis is the most frequent complication. Pyopneumothorax has also been observed in a number of cases.

The mortality rate is high and the prognosis is serious.

Medical treatment is essentially expectant.

The most efficacious method of surgical treatment and the correct time for its application is yet to be determined.

TRANSPLANTATION OF TUBERCULOUS LYMPH NODES

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AND
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What we have to report is not so much an accomplished fact as a new experimental method—namely, the production of experimental disease by transplanting infected tissues into normal animals. Our own work with the method has consisted chiefly in the transplantation of tuberculous lymph nodes, as we have hoped in this way to get evidence on the question whether lymphoid tissue has a deterrent effect on the tubercle bacillus.

The procedure has been simple—possibly too simple. We first infected a number of guinea-pigs with human tubercle bacilli by subcutaneous injection. After about a month, when the inguinal lymph nodes were well enlarged, we removed these and planted them beneath the abdominal skin of healthy guinea-pigs, through a small incision which we afterward sewed up. These pigs becoming infected in turn, their inguinal nodes were planted in a new group, and so on.

The typical course of the experiment is as follows: The incision heals clean in about two weeks, the node remaining in place without inflammation. If the pig is killed at the end of the first week the planted node is found to be still free, and if the node happens to slough out in this phase the host usually escapes infection. But during the second week, granulation tissue of the host becomes adherent to the planted node and new bloodvessels from the host begin to grow into its substance. The tissue of the node itself,

however, becomes necrotic, and the continuity which is established is between the host's healthy tissue and a source of infection. From the third to the fifth week, usually in the third, the host's inguinal nodes become enlarged, there is ulceration over the planted node and general progressive tuberculosis develops at a rate which seems to depend chiefly on the number of bacilli available in the planted node.

In this and other respects, the method gives results which, so far as we have gone, seem practically identical with those observed in infecting with free bacilli. The tuberculin reaction remains negative until enlarged inguinal nodes give evidence of active tuberculous lesions in the host's own tissues. A second tuberculous node planted in an animal which has already received and retained one will ulcerate through the skin, discharge and heal, like a second ulcer produced by injection of free bacilli, and will do this repeatedly as caseation progresses; but the ulcer over the first node never heals. We are forced to the conclusion that the tissue which we plant does not function either as a check to infection or as a true primary lesion, but merely as a vehicle.

We have tried planting other infected tissues, as pieces of spleen and liver, but the result seems essentially the same. It would be well to transplant whole infected organs, with proper surgical technic, but we have not attempted this.

The procedure described was the basic experiment. We are trying to modify it so as not to subject the host to infection, but only to products of infection in the planted node. With this object we have coated tuberculous nodes with collodion and then planted them. We have not gone far enough with this to say much about it, except that it is certain that both albuminous and fatty substances pass through these membranes and bacilli do not. The bacilli within these coated nodes seem to die out in a short time. We have no proof as yet that substances toxic to the tuberculous animal pass through, but inflammatory reactions following the planting of coated nodes in some tuberculous animals suggest this.

We have made some experiments with other membranes, but collodion seems the most promising.

As stated, what we chiefly wish to present is the method. We feel that it is an instrument which can be adapted to many kinds of research, and hope that we, or others, may sometime do something useful with it, even in the stony field of tuberculosis. So far we have done little more than provide a new illustration for the thesis that in order to have increased immunity to tuberculosis one must have tuberculosis.

URINARY SIDEROSIS

Hemosiderin Granules in the Urine as an Aid in the Diagnosis of Pernicious Anemia, Hemochromatosis and Other Diseases Causing Siderosis of the Kidney

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NEW YORK

The siderosis produced in rabbits by transfusions repeated over a long period[1] has as one of its features a pronounced pigmentation of the kidney parenchyma comparable with that encountered in the hemochromatosis of human beings. Great numbers of yellow-brown granules which react positively for iron are present in the cells of the convoluted tubules and the loops of Henle. They are also to be found lying free in the lumen of the tubules and embedded in casts. This fact suggested a search for hemosiderin granules in the urine of patients with pigmentation of doubtful origin. A test case soon came to hand.

A soldier, aged forty-six years, was admitted to the Hospital of the Rockefeller Institute November 22, 1917. He complained of weakness, loss of weight, sugar in the urine, and swelling of the legs. One brother had died of diabetes at the age of forty-nine years. The patient himself had always been strong and well, save for appendicitis relieved in 1900 by operation. A Neisser infection in 1898 was followed by a stricture which yielded to treatment. Lues was denied. The present illness may be said to have begun in 1908, when, following three days of hard physical exertion, with loss of sleep, there occurred a sudden edema of the legs. The patient was in bed only a week, and the trouble did not reappear.

In December, 1916, the patient's friends noted that his skin was turning gray. He consulted a physician, who found sugar in the urine. Fasting, followed by a low diet, caused the sugar to disappear; and the patient's

weight and strength, which had somewhat diminished, were restored. He entered the army service in July, 1917, feeling well at that time, but soon began to have swelling of the feet and legs and shortness of breath. The division surgeon found sugar in the urine.

When admitted to the hospital for treatment by Dr. Allen, the patient was not very ill. He was lean rather than emaciated. The skin of the face and of the back of the hands was somewhat freckled and looked weather-beaten, but more notable was a uniform, light, dusky gray pigmentation of these parts. The remaining body surfaces had no unusual tint, and the mucous membrane of the mouth was normal looking.

Physical examination disclosed a myocarditis, an enlarged, firm liver, ascites, and well-marked edema of the feet and legs. The arteries were thickened. The liver edge was 9 cm. below the costal margin in the millimeter line, very sharp and firm, and the surface of the organ was smooth, hard, and somewhat bulging. The spleen could not be felt. There was a well-marked scar on the glans penis, but the Wassermann reaction was negative. The knee-jerks were absent. The urine showed a large amount of sugar, but the ferric chloride test was negative. No albumin or casts were found.

The blood-pressure was very low and so remained throughout the several months of hospital observation, ranging between 80 and 104 mm. systolic, and 46 to 70 mm. diastolic. There was a slight anemia: a hemoglobin averaging 95 per cent. Sahli, with 4,400,000 red blood corpuscles per c.mm. Reticulated cells were rare on the one examination made, averaging 1 per thousand.

The diagnosis lay between syphilis, favored by the venereal history, genital scar, thickened vessels, absence of the knee-jerks, and perhaps also by the enlarged liver, and the diabetes; Addison's disease, as indicated by the pigmentation, low blood-pressure, and asthenia; and hemochromatosis, suggested by the combination of enlarged liver, pigmentation, and diabetes. Addison's disease was judged to be most likely.

Urinary Findings. A fresh specimen of the urine was centrifugated and the slight sediment examined for hemosiderin. It consisted almost entirely of large cells containing numerous coarse, yellow-brown granules (Figs. 1 and 2). Often these granules were as big as red corpuscles, and had then the appearance of having been formed out of several smaller lumps. They were solid looking, moderately refractile, and of irregular shape, in distinction from the rounded, smooth globules of greenish-yellow fat, sometimes

met with them. Many of the cells were breaking down, and numerous free granules and larger lumps of the pigment were noted. All, both free and intracellular, turned a brilliant black when submitted to ammonium sulphide, blue with potassium ferrocyanide and hydrochloric acid, and blue too in fixed specimens treated according to Nishimura's method.[2] There could be no doubt that they were composed of hemosiderin. The urine contained no blood, bile, urobilin, albumin, or casts.

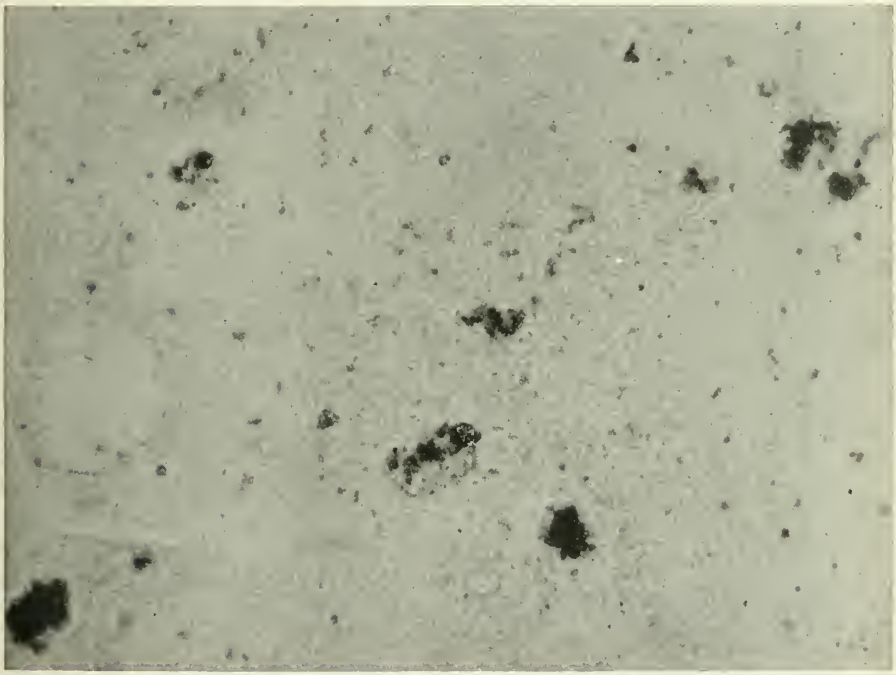


FIG. 1.—Free and intracellular hemosiderin in the urinary sediment of a patient with hemochromatosis. Nishimura stain.

The examination of the urine was repeated many times during the next three months. The output of hemosiderin granules was regularly abundant and cells heavily pigmented with them were always obtained in large number from 20 c.c. of urine. Control specimens from forty-four patients variously ill were searched for iron by the same methods. With one exception, which may be

attributed to artefact, intracellular hemosiderin was found only in diseases involving, like *diabète bronzé*, a true siderosis of the kidney parenchyma. The diseases referred to are pernicious anemia and chronic hemolytic jaundice. In view of these results, the diagnosis of hemochromatosis seemed warranted in the case just described.

FIG. 2.—Drawing of an actual field in a fresh preparation of the same sediment as in Fig. 1. The large size and ir egular shape of the pigment granules should be noted.

AUTOPSY FINDINGS. The patient died on April 3, 1918, three months after hemosiderin had first been recognized in the urine. Treatment had caused the urinary sugar to disappear promptly and permanently, but hyperglycemia had persisted. There was a gradually increasing edema of the legs and scrotum, with ascites and double hydrothorax; and death ensued from cardiac insufficiency. In the last weeks of life the cutaneous pigmentation became slightly more marked.

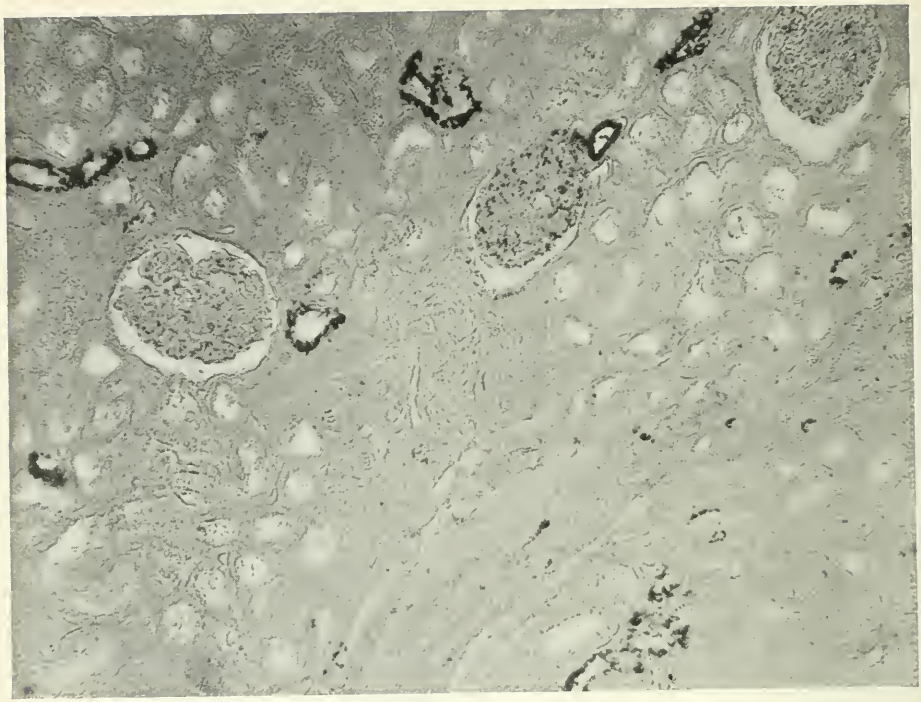
An autopsy, one and one-half hours after death, performed by the author, disclosed the characteristic lesions of hemochromatosis. The anatomical diagnosis was as follows:

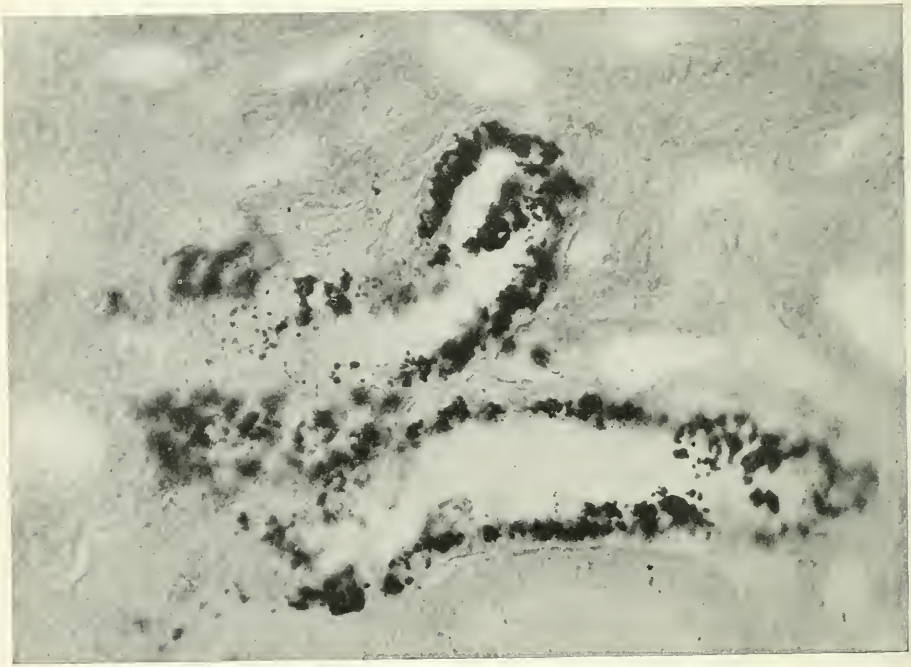
Myocarditis; hemochromatosis with pronounced pigmentation of the liver, pancreas, heart, abdominal lymph nodes, spleen, kidneys, thyroid, mesentery, skin, and other organs; cirrhosis of the liver and pancreas; chronic passive congestion of the liver, spleen, and intestines; ascites; hydrothorax; anasarca; fresh infaret of the lung; old infarcts of the kidneys.

The condition of the kidneys has special interest. There were present a few scattered, wedge-shaped areas of local atrophy and connective-tissue overgrowth, the result of old infarcts. The general siderosis, though pronounced, was limited to certain groups of cortical elements, notably the distal convoluted tubules (Fig. 3). Here the parenchymal cells were heavily laden with iron-containing pigment, and some had desquamated, while others had broken down *in situ*, liberating pigment granules into the lumen of the tubules (Fig. 4). The cells of the ascending portion of Henle's loop was also pigmented, but less so; and in many of the glomeruli were cells containing numerous fine, hemosiderin granules. The remainder of the kidney was non-pigmented, save for occasional free cells and granules in the lumen of the collecting tubules. The distribution in the organ of the hemosiderin was precisely that which Gaskell and his associates[3] have described and deem characteristic of hemosiderosis.

Method of Search for Hemosiderin. The following routine method of search for hemosiderin in the urine has proved satisfactory.

A fresh specimen of the urine, preferably warm from the body, is centrifugated at high speed and the supernatant fluid poured off as completely as possible. The sediment is suspended in the trace of fluid that remains, and slide preparations are gone over microscopically for suggestive orange or brown granules, more particularly in the cells. A mechanical stage should be used and ten minutes at least given to the search. As a rule the sediment from a 20 c.c. specimen will yield a fair number of cells from the higher portion of the urinary tract, but often that from 60 to 100 c.c. must be obtained. Occasionally, in urine allowed to cool prior to centrifugation, the nubecula is copious and prevents proper concentration of





Figs. 3 and 4.—Kidney of the patient with hemochromatosis. Nishimura stain. In Fig. 4 pigmented cells and free granules can be seen lying free in the lumen of a tubule.

the formed elements. When this is the case, a specimen should be centrifugated as soon as voided. Kept urines which have become cloudy with urates may be cleared by warming. To search a heavy crystalline sediment, or one poor in cells, or containing only leukocytes and squamous epithelium, is time wasted. Catheterized specimens are necessary from female patients, since hemosiderin may come into the urine from the genital tract.

The remainder of the sediment is suspended in a fresh mixture of 5 c.c. each of 2 per cent. potassium ferrocyanide and 1 per cent. hydrochloric acid. After ten minutes it is thrown down with the centrifuge, the fluid poured off as before, a drop of the sediment mixed on the slide with a drop of the hydrochloric acid solution, and a cover-slip put on. By this modification of Perl's reaction the cells are well preserved and are largely cleared, as are the granular casts. Often the hemosiderin will begin to turn blue as soon as the acid has been added, but if not the preparation should be looked at repeatedly in the course of the next half-hour. Usually there is present a little foreign debris which turns blue, giving an indication of when a positive finding may be expected. As in the case of the fresh sediment at least ten minutes of search should be given to the preparation.

The use of a more certain method to demonstrate iron, namely, that of Nishimura,[2] is often necessary. It is well known that hemosiderin in the tissues frequently fails to yield Perl's reaction, or to turn black with ammonium sulphide. This is likewise true of urinary hemosiderin. In several pernicious anemia cases suggestive looking orange granules were seen in the fresh, urinary sediment which proved refractory to the ordinary tests but were promptly shown to be iron-containing by the Nishimura procedure. The examination of fresh sediment assumes in this relation considerable importance as indicating that the search for iron should be persevered in. On the other hand, a failure to find suggestive pigment in the fresh specimen does not rule out the presence of iron. The ferrocyanide test has several times disclosed intracellular iron granules so minute and so surrounded by fat globules as not to attract attention in the fresh specimen. By Nishimura's method such instances are found even more often.

For the Nishimura test the fresh sediment, as free as possible from urine, is mixed with a little human serum untinted with hemoglobin, and thick films are made and dried. These are fixed by heat, placed in strong ammonium sulphide for one hour, washed briefly with water, and subjected for twenty minutes to a fresh mixture of 2 per cent. potassium ferrocyanide and 1 per cent. hydrochloric acid in equal parts. After another brief rinsing with water the preparations are stained in lithium carmine for a few minutes, differentiated in acid alcohol (1 per cent. hydrochloric acid), and run rapidly through 95 per cent. alcohol, absolute alcohol, xylol, and mounted in balsam. The acid alcohol differentiates the red of the carmine

and turns the iron granules a deep blue. Its action should be carefully followed with the microscope, since if prolonged it will dissolve the iron, or at least cause the blue tint of the latter to run and fade. Nishimura carried out two separate differentiations with acid, the first immediately after the ferrocyanide in order to bring out the blue of the iron reaction. But under these circumstances the subsequent action of the acid alcohol tends to destroy the blue color. A single differentiation is more satisfactory.

By this method permanent mounts are obtained to be looked over at leisure. The iron granules stand out in deep blue against the general carmine tint. Less satisfactory preparations may be had by submitting the films to ammonium sulphide and staining thereafter with carmine. Such hemosiderin granules as may react with the sulphide will then appear black. They lose their color rapidly in acid alcohol, so differentiation of the carmine should not be attempted with it.

Specimens left with preservatives prior to examination have proved unsatisfactory. Toluene permits autolysis of the cells, and formalin renders hemosiderin refractory to the ferrocyanide test and at length dissolves it. We have repeatedly found specimens which were negative, preserved with formalin and known to contain iron. Acid also dissolves the pigment, and it need not be looked for in very acid urines save when freshly voided. In old ammoniacal specimens it is remarkably stable and may persist undissolved for several days.

Findings in Pernicious Anemia. The urines were examined of ten undoubted cases of pernicious anemia. In an eleventh case no proper search for iron could be made because of the heavy sediment of pus corpuscles, etc., incident to a cystitis. In two instances no hemosiderin was found. Repeated search was made of specimens from one of these having the history of a year's illness and a moderate anemia (red blood corpuscles 3,160,000; hemoglobin 69 per cent. (Palmer)). In the other case the disease had lasted three years, during which period seventeen transfusions had been given. A single specimen only was searched for iron.

Intracellular hemosiderin was found in the urines of all the eight remaining instances, though not always easily. In two a careful search was necessary of specimens stained by the Nishimura method. The cells containing iron were very few and the pigment granules minute (Figs. 5 and 6). In a third instance Perl's reaction, applied to the fresh sediment, disclosed fairly frequent cells containing many fine, blue granules, half-obscured amid fat droplets. In the five remaining instances a surprisingly large amount of hemo-

siderin was found (Figs. 7, 8 and 9). It attracted attention at once in the unstained sediment. Multitudes of fine, brownish or orange-yellow granules were seen, grouped in cells, scattered in casts, and more particularly lying free in large numbers. Save in one case, they were much smaller than in the urine of the patient with hemochromatosis already described, as would naturally follow, from the relative intensity of the siderosis in the two diseases. From one to fifty or more granules were present in a single cell. They were spherical and remarkably regular in size in different specimens from the same patient, being usually somewhat smaller

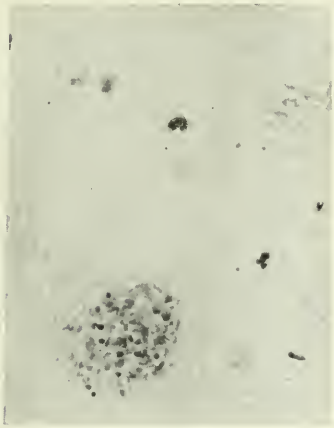


FIG. 5

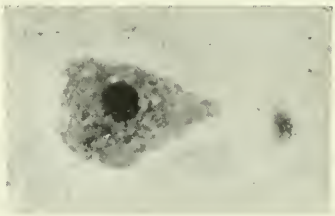


FIG. 6

FIGS. 5 and 6.—Minute hemosiderin granules in the urinary cells of a case of pernicious anemia. Nishimura stain. × 1060.

than eosinophile granulations. Occasionally they had cohered into lumps. The cells containing them were irregularly globular or cylindrical, slightly larger than leukocytes, as a rule, with a vesicular nucleus of moderate size. Often they were much degenerated and contained myelin or fat. In two cases the modified ferrocyanide test caused the entire sediment to turn bright blue to the naked eye. With the microscope the color was found to be localized in innumerable, sharply defined, deep blue granules. In the other instances with abundant hemosiderin the response to the test was only partial, a few of the granules turning blue or green. But

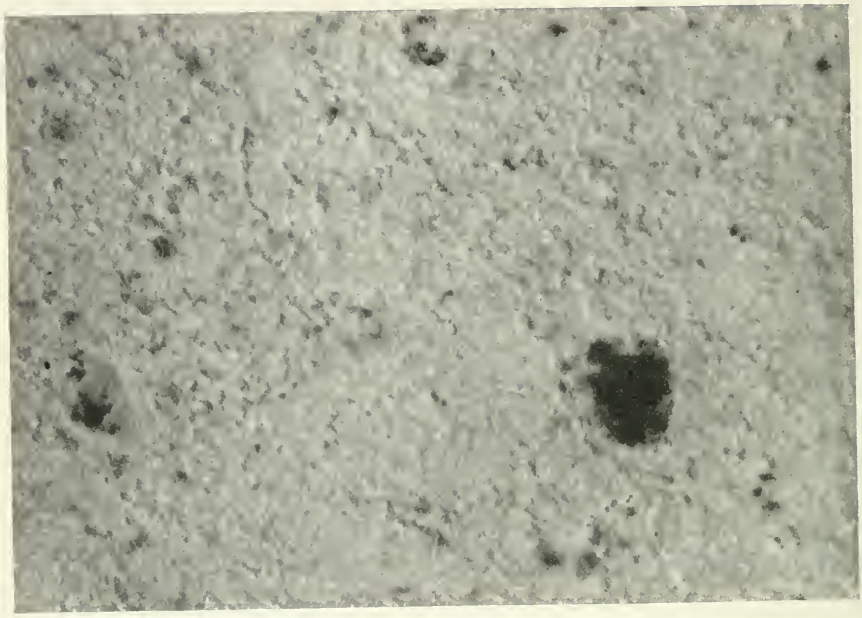


FIG. 7

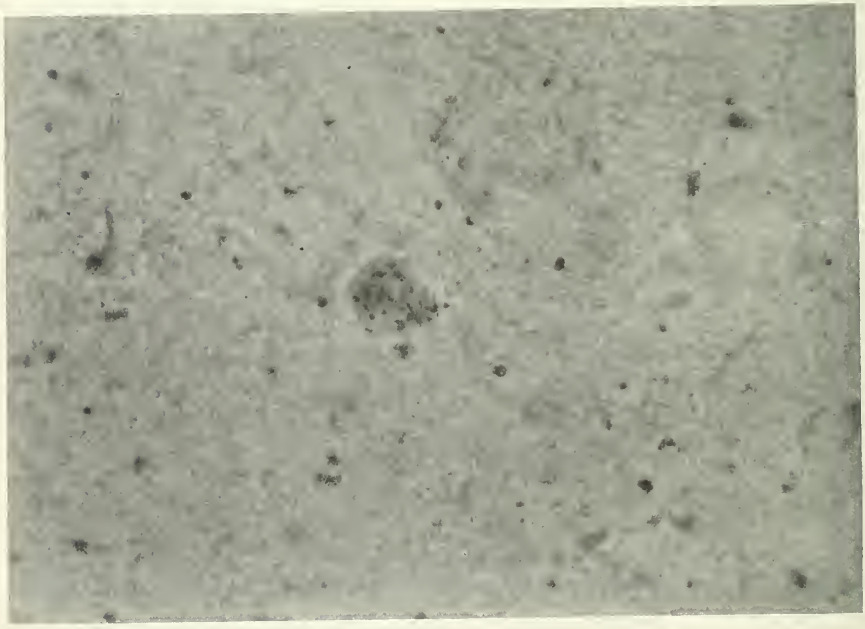


FIG. 8

FIGS. 7 and 8.—Hemosiderin, free and intracellular, in the sediment from a patient with pernicious anemia. The abundant pigment has the form of rounded granules. One of the cells of Fig. 7 is so crowded with it as to appear almost black. The amount of free pigment is noteworthy.

with the Nishimura method all of the pigment was shown to be iron-containing.

Hemosiderin was never found in the squamous epithelium or in tailed cells from the bladder. Part, at least, of what was free in the urine obviously came from disintegrating cells. Indeed, the presence in the fresh sediment of small aggregates of orange-yellow granules held together by a remnant of cytoplasm proved significant. In the casts the granules were ordinarily few and widely separated.

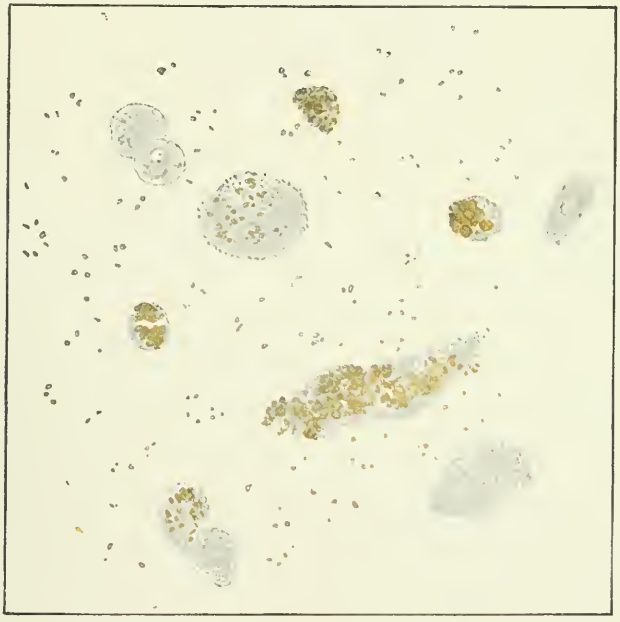


FIG. 9.—Drawing to show the appearance of the hemosiderin in fresh preparations from a pernicious anemia case. The cells are taken from several fields. Note the many free granules.

A few of the urines showing iron in quantity had the deep, smoky color and the general characters usual in severe pernicious anemia. Others were pale, free from albumin, and seemed normal. No definite relationship could be worked out between the output of pigment granules and the duration and severity of the disease. The fact that pernicious anemia may long exist unsuspected has

not improbably much to do with this. The findings in the individual case were remarkably constant from day to day. In one very sick patient, followed through two and one-half months, the hemosiderin output remained abundant. This was the exceptional case above mentioned, in which the granules were almost as large and abundant as in the patient with hemochromatosis.

FIG. 10.—Masses of free granular hemosiderin in a urine with scarcely any of the intracellular pigment. The specimen is from a case of pernicious anemia. Nishimura stain. × 1000.

FINDINGS IN HEMOLYTIC JAUNDICE. Through the courtesy of Dr. George Minot, of Boston, it was possible to examine the urine of a carefully studied, typical case of hemolytic jaundice of the acquired type. The patient, a male, aged twenty-eight years, had been more or less jaundiced since the age of sixteen, following what he understood was an attack of malaria with enlarged spleen. The spleen is still greatly enlarged, but the jaundice is slight, the health excellent, and the blood in good condition. At the time when the urine was searched for iron the blood showed a hemoglobin of 102 per cent. Sahli, but the red cells were rather unequal in size, with many macrocytes and about 6 per cent. of reticulated corpuscles. In the urine free hemosiderin was present in quantity, and there were numerous cells stippled with it. Most of the pigment responded readily to Perl's test. The intracellular granules were small, about the size of those usual in pernicious anemia, but much of the free pigment was in coarse, brown lumps. A cast was seen so colored with these as to resemble a miniature cigar.

FINDINGS IN CONTROL CASES. In none of thirty-three control cases, many of them with blood derangements, were such findings as the above obtained. In the fresh urinary sediment the numerous rounded, free, orange or brown granules were lacking, save in one notable instance to be discussed farther on, and clumps of them

held together by disintegrating cytoplasm were never observed. Pigmented cells, on the other hand, were fairly common. Often they were tinted a diffuse yellow or contained many fine, superimposed, greenish-yellow fat droplets. Large yellow or orange-brown globules were also encountered sometimes. In general they were of a fatty or lipoid nature, as indicated by their high refractility, smooth outline, resistance to acid, variation in size, and as proved finally by the Scharlach R stain. But occasionally intracellular granules were seen, indistinguishable in the fresh from hemosiderin but negative to microchemical tests. According to Aschoff,[4] an orange pigment, which fails to react for iron, is often present in the kidney cells of old people. A very fine crystalline deposit, furthermore, may simulate hemosiderin granules, free and in casts. Siderosis of the urine cannot be recognized with certainty from the fresh specimen alone. Microchemical tests must always be employed. In this connection it has been interesting to discover that Hunter[5] in 1889 published a note on the granular pigmentation of the cells and casts in the urine of a patient with pernicious anemia. From his description there is no reason to doubt that he had to do with a true siderosis, as was his own conviction. But he made no attempt to demonstrate iron by microchemical tests or to examine the urine of controls. His observation has never been followed up, probably because orange and brown granules are so frequently encountered in urines taken at random.

In one control urine a single cell was found containing iron in the form of several coarse lumps which gave Perl's reaction readily. The urine was an uncatheterized specimen from a woman with a poorly compensated cardiac lesion. No free hemosiderin granules were seen, and a second specimen carefully searched was entirely negative, as was the urine of several other heart cases. In view of the character of the granules and the general circumstances of the case it seems probable that the cell came from the genital tract. The finding emphasizes the necessity for catheterized specimens from female patients.

In another control instance much free hemosiderin was present in the urinary sediment but none in the cells. The patient had a chronic nephritis in the terminal stage with extreme anemia and

constant slight bleeding from the mucous surfaces. The urine, of pale straw color, gave a weakly positive guaiac reaction, and a small number of red cells were present in the sediment. This latter contained numerous aggregates of very fine, rounded, slaty brown granules, which reacted positively to the test for iron. In a second and catheterized specimen obtained two days later no red cells or shadows were seen, and there was only the faintest blue coloration on test with guaiac, yet the clusters, or aggregates of hemosiderin granules were still present. The most careful search failed to reveal any cells containing such granules.

Some of the control cases deserve special mention. Three had the diagnosis of pernicious anemia on admission to hospital treatment, at which time the urine was examined. All had an extremely severe anemia, necessitating transfusion, a high color index, and in two instances a profusion of nucleated red cells were in circulation. One of the cases, that of chronic nephritis, has just been discussed. The other two, with urines negative for both free and intracellular hemosiderin, proved on study to be instances of secondary anemia, one subsequent to a severe purpura, the other associated with chronic malnutrition. The urinary findings were negative also in a patient with chronic polycythemia, and in two instances of Hodgkin's disease with great progressive anemia.

Discussion. The presence of hemosiderin granules in the urine seems to have been overlooked heretofore. It is advisable to make a sharp distinction between the intracellular and free pigment, since there is probably a difference in their significance. True, when the granules are found inside urinary cells, free granules are regularly present also, and usually in far greater number. But free hemosiderin has been found alone in the urine of a nephritic patient whose condition presumably did not involve siderosis of the renal cells. Furthermore, extraneous material may easily be mistaken for free hemosiderin by the inexpert. Bits of foreign detritus frequently respond to the test for iron. As a rule, they are coarse and very different in appearance from the finely granular, true pigment.

The free hemosiderin granules occurring in the urine of patients with a true siderosis of the kidney are obviously of intracellular

derivation as a rule. The granules have the size and appearance of those in the accompanying cells, and often a remnant of cytoplasm is attached to them or holds together a number of them in its matrix. The rest lie scattered broadcast in the sediment. In one instance, though, the free hemosiderin was of very different character, resembling that in the urine of the nephritic above mentioned. The granules, which were extremely minute, formed aggregates or clusters, sometimes of many hundreds, lying here and there in the urinary sediment (Fig. 10). Intracellular granules were rare. The findings varied little from day to day. The patient, a woman with severe pernicious anemia, had not been transfused, and there was no blood in the urine (guaiac reaction). A possible origin of the pigment from the genital tract was ruled out by catheterization. The inference would seem to be that in this case, as also in the nephritic, hemosiderin was circulating in solution within the body and was directly excreted by the kidney. This assumption is contrary to the general view, according to which during life hemosiderin arises only in cells, and as a granular solid limited to them or their neighborhood.[6] The problem presented is now under investigation in animals.

The evidence seems convincing that the presence of cells containing hemosiderin in urine obtained under proper precautions is the expression of an actual siderosis of the kidney parenchyma. These cells may be found in most instances, if not all, of diseases that involve such a condition. Fortunately the diseases are few and are readily distinguished from one another, whereas those with which they are oftenest confused produce no renal siderosis. The presence of intracellular hemosiderin in the urine assumes in this light importance for diagnosis.

On *a priori* grounds one may predict with some confidence that the examination of urinary cells for iron pigment will prove to be a decisive method of determining the presence of hemochromatosis in doubtful clinical instances of cutaneous pigmentation. For in hemochromatosis the siderosis of the skin is far surpassed by that of the internal organs. In hemolytic jaundice, congenital or acquired, the history, clinical features, and condition of the blood amply suffice for diagnosis; and the presence or absence of hemosiderin in the urine has interest merely as indicating the condition

of the internal organs. In some of these jaundice cases no siderosis of the kidney is found at autopsy.[7] The exact bearing of the urinary findings on the diagnosis of pernicious anemia will require many observations. Positive findings cannot be expected in early stages of the disease before siderosis is established. But do cases come into the physicians' hands then? Observations on the urine will throw light upon the point. This much, at least, is already certain, that a positive finding in the urine has significance for the diagnosis of pernicious anemia, whereas a negative one may have none. Even in advanced cases of the disease, as the present work has shown, cells containing hemosiderin may be so rare as to require, by the rather crude methods described, a persevering search for their discovery. Iron pigment is known to be relatively stable, once it has been deposited in the tissues. But whether it will persist sufficiently in the kidney—and the urine—to be useful in diagnosis during the remissions of pernicious anemia remains to be seen.

Besides the diseases mentioned, certain local or general conditions, fortunately rare, may conceivably lead to a urinary siderosis. Severe, long continued hemolysis of any kind, as for example that from malaria, may be expected to do so. According to Aschoff[4] a patchy siderosis of the renal parenchyma sometimes results from local hemorrhages. Furthermore, according to the same authority, hemoglobin excreted into the tubules may be taken up again by the living cells and converted into hemosiderin. Urinary siderosis becomes a possibility, therefore, in paroxysmal hemoglobinuria, or after the transfusion of incompatible blood. Finally, hemorrhages into the mucosa of the urinary passages may perhaps lead to a desquamation of iron-containing cells.

All but two of the pernicious anemia cases examined in the course of the present work had been transfused, some of them many times. One of the two untransfused patients had much hemosiderin in the urine, and the other none. The influence of successful transfusion to induce of itself a renal siderosis must be considered, since in normal animals transfusions frequently repeated over a long period undoubtedly have this result.[1] But the findings in transfused human beings who were among the controls in the present work are in agreement with the results in animals in showing that much

alien blood may be introduced into the body before any renal siderosis develops. The urines of these clinical controls, some of whom had been many times transfused, were uniformly negative for iron-containing pigment granules. In one case, that of a girl, aged fourteen years, with purpura, nine transfusions, totalling 6000 c.c. of blood, had been given in the month prior to the urinary examinations. Yet the urine, searched on several occasions, proved completely free from hemosiderin. The physiological conditions are different in pernicious anemia. Here transfused blood is in the end just so much more material to be destroyed in the course of the disease, with a resulting increased retention of blood derivatives. That siderosis may be enhanced thereby can scarcely be doubted.

The circulating leukocytes in the case of hemochromatosis were, in general, free from hemosiderin. Several examinations were made, using thick films of washed leukocytes stained for iron by Nishimura's method. After long search one cell was found containing a few small, blue granules.

Summary. In diseases which bring about a siderosis of the kidney there are ordinarily present in the urinary sediment cells containing granules of hemosiderin, and often many free granules as well. The finding has proved useful in the diagnosis of hemochromatosis and will probably be of service in the recognition of pernicious anemia, and possibly some other diseases. But in this relation the fact should be emphasized that urinary siderosis, as one may term it, is the indication of a renal condition, not of a disease.

My special thanks are due to Dr. Walter W. Palmer, to Dr. George Minot, of Boston, and to Dr. Edward Lindeman, for their kindness in providing the clinical material essential to the work.

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IMMUNITY IN CANCER

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The two main problems in cancer are those of *causation* and *cure*. One of the obvious means of obtaining a cure is the induction of an immunity against the cancer cell, and reasoning from the analogy of bacteriological immunity, such resistance ought to be obtainable. Unfortunately, however, the analogy has proved on investigation not to be applicable in cancer.

The idea of immune processes affecting malignant tumors in man arose from the occasional occurrence of spontaneous disappearance of neoplasms, either following infections, especially by the streptococcus, after slight operative procedures, or even without any outside interference at all. There is no evidence, however, that spontaneous cure is due to immunity.

The hypothesis that an immunity to cancer exists was strengthened:

1. By the observation that implanted tumors in mice and rats might regress, often leaving the animals resistant to further implantations. The important fact was overlooked that implanted tumors and spontaneous tumors are not comparable and that regression in spontaneous tumors is as rare in mice as in man.

2. The production of resistance to transplantation after injection of homologous tissue, also, led to the hope that immunity to tumor growth might be obtained.

3. Additional confusion was produced by the loose transference of ideas of bacterial immunity to the hypothetical immunity in cancer, for it was not realized that in one case the cell is a

foreign parasite, while in the other it is native to the host which carries it.

These three notions have led to extensive series of experiments, using heated cultures of bacteria, bacterial toxins, human blood serum from infants and adults, extracts or emulsions or implantations of fetal or adult tissue, vaccines of ground cancer tissue, either autologous or heterologous, and, finally, immune sera prepared by treating animals with cancer tissue. All these forms of treatment are without the slightest effect on the progressive growth of malignant tumors, though the failure to produce specific organ cytotoxins might have prepared us for the failure of cancer cytotoxins.

A second phase of research for a cancer immunity was based upon the study of the morphological changes occurring when tumors or normal tissues regress after implantation in a suitable host, which showed that the process is often, though not always, accompanied by the collection of a lymphocytic exudate surrounding the graft, such as has long been observed about slow-growing human tumors.

The first and most obvious step was to attempt by the injection of large amounts of lymphoid tissue to influence the tumor growth. A number of discordant reports exist in the literature, but the repetition of the experiments at the Crocker Fund laboratory on a scale large enough to remove experimental fluctuations has shown that no effect is observable. Neither is the reverse true, that excision of the spleen, an important lymphoid organ in mice, facilitates tumor growth.

Inasmuch as bleeding has been shown to stimulate the production of immune antibodies, and even of autologous immune substances, such as agglutinins, as was recently shown by Robertson and Rous, attempts have been made to stimulate by this procedure the normal resisting power of animals and even of human beings to tumor growth. This has, however, been without effect, a result which might have been expected, since it was shown some time ago that the injection of autologous tissue produced not only no immunity to cancer growth (Haaland), but none even to transplantation (Woglom).

Again, although it has been conclusively shown that the cells of another species do not produce immunity even to transplantation, yet the conclusion has been drawn that the development of the hematopoietic system of the chick embryo was the reason for the disappearance of tumors engrafted on the membrane. The lack of any causal relationship between such disappearance and the hematopoietic system has been demonstrated in the Crocker Fund laboratory. The real reason for the disappearance of the tumor, if it does disappear, is the production by the fetus of antibodies against the foreign protein. A highly potent tumor will grow for a very considerable time in a foreign host; for example, the Crocker Fund mouse tumor No. 180 exceptionally will grow for from thirty to thirty-five days in a rat; most of the tumors, however, disappear at the time when the ordinary antibodies—cytolytic, cytotoxic or what not—appear at their peak, that is, in from ten to fourteen days. The production of antibodies is inhibited by *x*-rays, and Murphy believes that such heterologous implants live longer in *x*-rayed animals. This type of immunity is, of course, of no interest in the study of the cure of human cancer, as any immunity to be useful must be autologous and not heterologous.

Da Fano and Bashford cautiously suggested, from morphological studies alone, that possibly the lymphocytes might be carriers of immune substances, inasmuch as they collect about regressing tumors. Loeb, also, laid stress on the destruction of transplanted normal tissues by increased activity of the small mononuclear cells. This view has been upheld by others, including Murphy. The fact that lymphocytes in man collect chiefly about slow-growing tumors and not about the highly malignant forms, together with the additional fact that metastases are frequent in lymph nodes, in my opinion has not been given sufficient weight.

To test the matter the following work has been done at the Crocker Fund:

In the first place, preliminary investigations of the blood of white rats and mice showed that great caution must be exerted in considering any particular count a norm. One hundred per cent.

fluctuations from day to day or from week to week were not infrequent, and great differences in cell-type percentages also were observed.

1. Assuming that the lymphocytes carry protective substances, mice with lymphatic leukemia or very high leukocyte counts, 20,000 to 30,000, should show some immunity to tumors. This is not the case. Sittenfield, also, was not able to show that an artificial lymphocytosis had any effect on tumor growth.

2. If grafts of normal tissues are destroyed by lymphocytes, a preliminary reduction of the total leukocyte count, especially by means of *x*-rays or radium, should result in a greater number of takes. This we have not been able to demonstrate, even when many hundreds of grafted animals and controls were used.

3. In this same connection it was important to determine whether a tumor of very low growth potentiality could be influenced by the destruction of the lymphocytes. Such a tumor is a guinea-pig fibrosarcoma now being transplanted in the Crocker Fund laboratory. The percentage of takes in this tumor is very small. The animals were *x*-rayed previous to and following the inoculation of the tumor, the site of the growth being protected by lead. No increase in the number of takes was observed.

4. The effect of the reduction of the lymphocytes in the circulating blood on the rate of take of tumors was studied, first with transplanted tumors, secondly with primary tumors inoculated into a series of animals, half of which were rayed, the raying being either very light or very heavy. Not the slightest difference could be observed over a considerable series of experiments between the rayed and the not-rayed animals.

5. Finally, the raying of rats in which a highly virulent mouse tumor had been implanted did not prolong the life of the tumor.

It is therefore evident that the lymphocyte is in no way correlated with cancer immunity.

Inasmuch as all the serological reactions—precipitins, agglutinins and complement-fixation—are not produced in either human or animal hosts bearing the tumors, it is plain that so far it is impossible to speak at present of a true immunity to cancer. All we know is that it is possible to produce an immunity to implantation

from one animal to another. If we could extend this immunity so that it would be possible to prevent the implantation of tumors of the host in his own body, an important advance would be made in the therapeutics of cancer, because this would check metastasis. But as yet we have not reached even this point.

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EXPERIMENTAL HEMOCHROMATOSIS

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In pernicious anemia and hemochromatosis an iron-containing pigment, hemosiderin, ordinarily derived from hemoglobin, is deposited in organs free from such pigment in most conditions that involve blood destruction. When sudden hemolysis takes place in a previously healthy human being, as after cutaneous burns or the action of a "blood poison," hemosiderin granules appear in the spleen, the red marrow, and sometimes in certain lymph nodes, but as a rule in these organs only. A similar localization of the pigment is found in most diseases accompanied by a destruction of red cells—acute malaria, for example; and it is regularly encountered in animals submitted to experiments or infections which, like trypanosomiasis, involve a breaking down of blood. Far different is the siderosis of pernicious anemia and hemochromatosis. The spleen and bone-marrow are still pigmented, but to only a slight degree as compared with some of the other organs. In pernicious anemia most of the hemosiderin is found in the liver and much in the kidneys. In hemochromatosis the liver, kidneys, pancreas, heart, abdominal lymph nodes, and many other organs are heavily loaded with the pigment.

What is the cause for the difference thus outlined? Has the hemosiderin in hemochromatosis another source than the blood? These and other important questions suggest themselves. And numerous attempts to answer them through an experimental production of the significant lesions have already been made. Stadel-

mann,[1] Hunter,[2] Biondi,[3] and others obtained a siderosis of the liver parenchyma as the result of fatal doses of toluylenediamine. The drug injures the liver greatly. Schurig,[4] who injected pure hemoglobin into rabbits day after day for several weeks, found some hemosiderin in the liver and kidneys, in addition to the usual abundance in spleen and marrow. Muir and Dunn,[5] producing an acute hemolytic anemia in rabbits by means of a specific hemolysin, noted a little granular hemosiderin in the liver and a diffuse Prussian blue reaction in the kidney parenchyma of animals surviving the destruction in the course of three days of more than half their total blood. Other less successful results might be quoted. The general findings warrant the conclusion that under most circumstances of blood destruction the spleen and red marrow act as depots for hemosiderin and more than suffice for the purpose; but when the breaking down of red cells is fulminant, or large quantities of blood pigment are furnished the organism for a considerable period, the buffer activity of these organs is overcome, and some little hemosiderin is laid down elsewhere. There are several obstacles to obtaining a great deposition of it by experimental means. Free hemoglobin injected in considerable amount is for the most part rapidly lost through the kidneys; blood cells that are damaged tend to accumulate in the capillaries and cause lesions; while the blood poisons, repeatedly administered, injure other tissues besides the blood, with complex results. In view of these circumstances the unsatisfactory outcome of experiments is easily understood.

Method. It has seemed to us that better results than those described might be obtained through a utilization of the animal's own ability to break down blood under circumstances such that more pigment is liberated than spleen and marrow can deal with. A means for the work has come to hand in the method of repeated transfusion employed by one of us with Robertson for the study of normal blood destruction.[6] Rabbits rendered plethoric by the day to day injection of 10 c.c. of the citrated whole blood of other rabbits soon acquire the ability to dispose rapidly of the foreign blood, and this in many instances without the development of demonstrable immune bodies. We have accordingly transfused

eleven animals for months, injecting them six days out of every seven, and toward the end increasing the daily amount of blood to 15 c.c. For each recipient a number of donors were used in rotation. In the early weeks some of the recipients developed weak agglutinins for the foreign blood. Later, as the injections were continued, such antibodies disappeared.

Findings in Relation to Pernicious Anemia. In the present paper a general description of the results of the work will be given. A study of certain of its special features is to be published later.

The rabbits killed after a few weeks of plethora induced by the repeated injections of blood showed merely the lesions already described by many observers[7] as following one or two massive transfusions; namely, an enlarged spleen, turgid with cellular debris and pigment, and phagocytes full of red cells; a considerable siderosis of the marrow; and a slight one of the abdominal lymph nodes—in other words, the findings usual after blood destruction in normal animals. When the injections had been kept up for two months there was in addition a pigmentation of the parenchyma of the liver and kidneys with fine yellow-brown granules which on test proved iron-containing. The pigment was abundant in the peripheral cells of the hepatic lobules and in the convoluted tubules of the kidneys, as is the case in pernicious anemia. Save for the siderosis, a general plethora, and a consequent slight, central atrophy of the liver cells, the organs appeared normal. In human pernicious anemia the spleen is relatively free from pigment, whereas in our animals this organ was most heavily loaded with it. The difference is an important one, indicating as it does either that the spleen is altered in pernicious anemia, and unable to take up the products of blood destruction, or that its activity is somehow circumvented, which is the supposition in Hunter's theory of a portal blood destruction.

Findings in Relation to Hemochromatosis. Seven rabbits were transfused over a period of from three to six and one-half months. The findings in these have great interest, for they are such as are associated, in human beings, with hemochromatosis and with this disease alone. Most of the animals were healthy when killed and had gained weight despite the long standing plethora which

involved a day to day hemoglobin of 120 to 160 per cent. Sahli, and as the autopsies showed a pronounced general congestion. Jaundice was not noted at any time, nor was hemoglobin or sugar found in the urine. The absence of the latter is accounted for by the state of the pancreas which showed lesions of a mild grade in contrast to the serious changes which accompany the *diabète bronzé* of man.

In comparing the rabbit material with that of human hemochromatosis, we have made use of the recent excellent descriptions of Sprunt[8] and Gaskell and his associates,[9] and also of specimens from an outspoken case of hemochromatosis studied at the Hospital of the Rockefeller Institute, and autopsied by one of us.[10] The older studies of hemochromatosis are in general marred by the use of unsatisfactory methods to demonstrate iron-containing pigment.

The changes in the rabbits were, in general, less marked than those observed postmortem in human hemochromatosis, as would naturally follow from the facts that the pigmentary process had not gone so far in the animals as even to menace health. Nevertheless, many of their organs, notably the liver, kidney, heart, visceral lymph glands, pancreas, spleen, and marrow, had, to the naked eye, a distinct brown tint. The liver was in several instances of a light chocolate color and showed a slight, diffuse cirrhosis, indistinguishable in the gross from that so frequently intercurrent in rabbits. The spleen was never larger than after several weeks of transfusion and often smaller. The skin of a long transfused white rabbit had a brownish tone. In every case the vessels were engorged, the liver was swollen, owing to congestion, and the heart was enlarged and dilated. The histological findings were essentially similar in all the animals, differing only in degree.

Pigments. Most of the pigment in the organs differed not at all in appearance or reactions from the hemosiderin observed in human beings. It had the form of orange brown, moderately refractile granules, usually minute, but sometimes coarse and irregular, as in the spleen. When exposed to ammonium sulfide the granules turned black, and when tested by Nishimura's method[11] they took on a fine, deep blue color. In determining their distribution to the various organs, we have regularly used the latter

method, which Sprunt and others, working with human material, have found satisfactory.

Hemofuscin, a yellow or brown pigment which fails to react for iron, occurs in quantity in some cases of human hemochromatosis, whereas in others it is practically absent. As Sprunt has pointed out, its amount varies greatly with the method used to demonstrate it. With the Nishimura test there is always far less than with Perl's reaction which the older authors generally employed for the demonstration of iron. The hemofuscin is to some extent characterized by its situation, being found especially in the capsules and trabeculæ of lymph nodes and in the smooth muscle of the walls of bloodvessels. Very little was present in the numerous preparations from our recent case of human hemosiderosis. In the transfused rabbits a yellow pigment which failed to respond positively to the Nishimura test was observed in scattered connective-tissue cells of the lungs and choroid plexus.

Comparison of the Human and Rabbit Organs. *Spleen.* The condition of the spleens of rabbits long transfused justifies the conclusion already expressed that this organ serves as a buffer depot for hemosiderin, and that its activity in this direction must be overcome if the pigment is to reach the other viscera in quantity. In animals killed after only three or four weeks of plethora the spleen was much enlarged, turgid with cellular debris and with phagocytes crowded with red cells. The liver and other viscera were at this period practically non-pigmented. But when the plethora had been maintained for months an entirely different state of affairs was found. The spleen, no larger than before, and often rather small, was a mere congeries of sinuses, containing large, irregular masses of hemosiderin, and distended with blood, but almost empty of other cells (Fig. 1). The Malpighian corpuscles were atrophic, and many had nearly disappeared. The organ was, in fact, a mere shell, scarcely to be thought of as functioning longer for the retention of blood pigment. And, as would naturally follow from this fact, the liver and many other organs now showed profuse deposits of hemosiderin.

In the hemochromatosis of man there is chronic passive congestion of the spleen consequent on the liver cirrhosis characteristic

of the disease. Phagocytes distended with hemosiderin are present in moderate number, but the greater part of the pigment, which at most is not abundant as compared with the amount in other organs, lies in the reticular cells. The Malpighian bodies are not atrophied. A diffuse increase in the connective tissue may usually be noted. There is no sign that a great activity of the organ to store up pigment was once present and has been overcome.

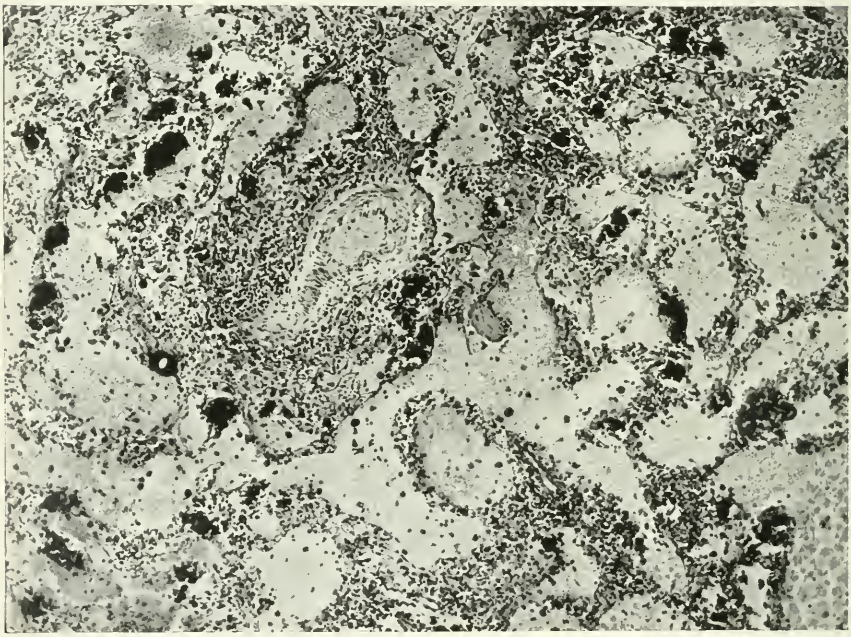

FIG. 1.—Spleen of a rabbit (A) transfused 139 times during a period of 167 days. The sinuses are distended with blood. An atrophic Malpighian corpuscle may be seen near the center of the photograph. The black masses consist of hemosiderin, for the most part extracellular.*

Bone-marrow. The marrow of the rabbit, after months of plethora from transfusion, showed little more pigment than after a few weeks (Fig. 2). Evidently the limit of its capacity for the reception of hemosiderin had soon been reached. The greater

* The sections from which Figs. 1 and 8 are taken were stained with methylene blue and eosin. Nishimura's method was used with all the other photographic material to demonstrate iron-containing pigment, and lithium carmine was employed as a counter-stain.

part of the pigment lay in distended mononuclear cells. The entire quantity was only moderate. In man, too, this is the case. No distinct changes in the blood-forming tissues are to be noted in either animal.

Liver. In the rabbits this was, after the spleen and certain of the abdominal lymph nodes, the most heavily pigmented organ. In one instance the degree of siderosis approached that in some

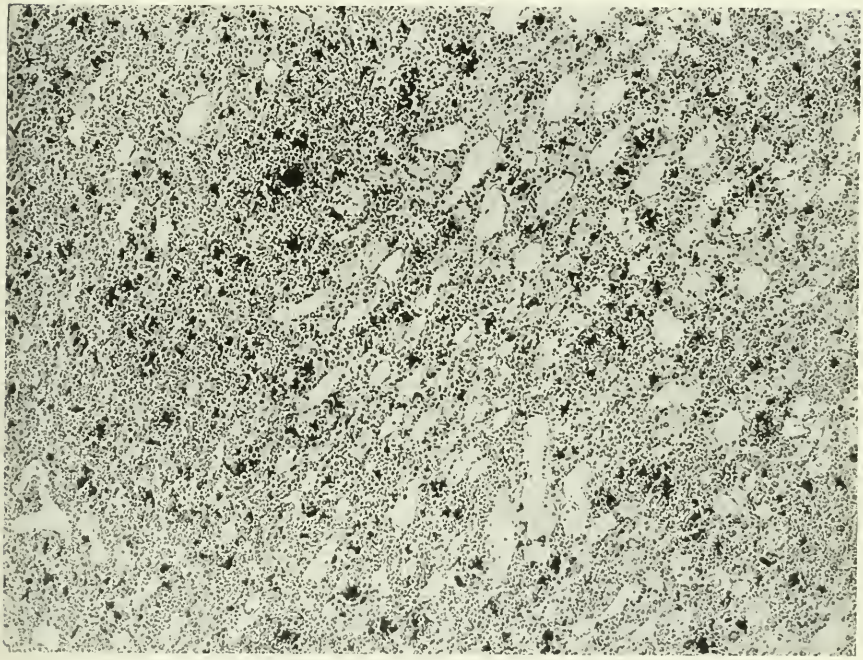

FIG. 2.—Bone-marrow of the same animal. The hemosiderin appears black, as is the case also in the photographs which follow.

patients dying of hemochromatosis (Fig. 3). The parenchyma everywhere contained numerous pigment granules, but notably at the periphery of the lobules, where often the cells were filled with coarse yellow lumps that turned dark blue when tested by Nishimura's method. Similar iron-containing pigment lay in the capillaries, much of it in great rounded masses enclosed more or less completely in multinucleate giant cells. Many Kupffer cells were filled with pigment granules. Toward the center of the lobules

the capillaries were widely distended, without doubt as a result of the plethora, and there was some pressure atrophy of the otherwise normal looking parenchymal elements. In two of the most pigmented livers there was some intralobular cirrhosis, but in a third this element was quite lacking, and careful study has convinced us that such cirrhosis as was found was intercurrent in

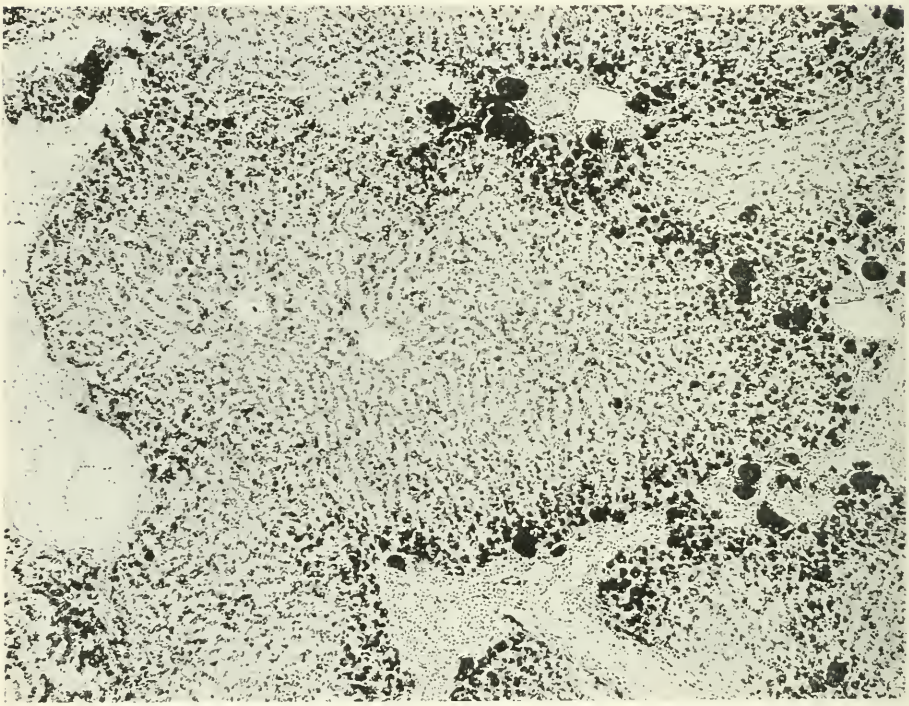

FIG. 3.—Liver of the same animal as in Figs. 1 and 2. The cirrhosis is intercurrent. The iron is especially abundant toward the periphery of the lobules, but the parenchyma shows granules of it everywhere.

character, of a sort frequently seen in supposedly normal rabbits. The question of its relationship to the pigmentation will be discussed in detail further on. The cirrhotic tissue contained some newformed bile ducts, but neither these nor the normal ones were pigmented, though here and there a connective-tissue cell was laden with the characteristic brown granules.

In man the siderosis of the liver parenchyma has the same general

appearance and an identical distribution with that in the rabbit, being more abundant toward the periphery of the lobules. Here many of the parenchymal cells may become so filled with pigment as to break down, resulting in connective-tissue proliferation and the appearance of islands of new-formed liver cells. There is regularly present a pronounced hypertrophic cirrhosis with many new-formed and heavily pigmented bile ducts. This characteristic feature of the human disease was absolutely lacking in our rabbits.

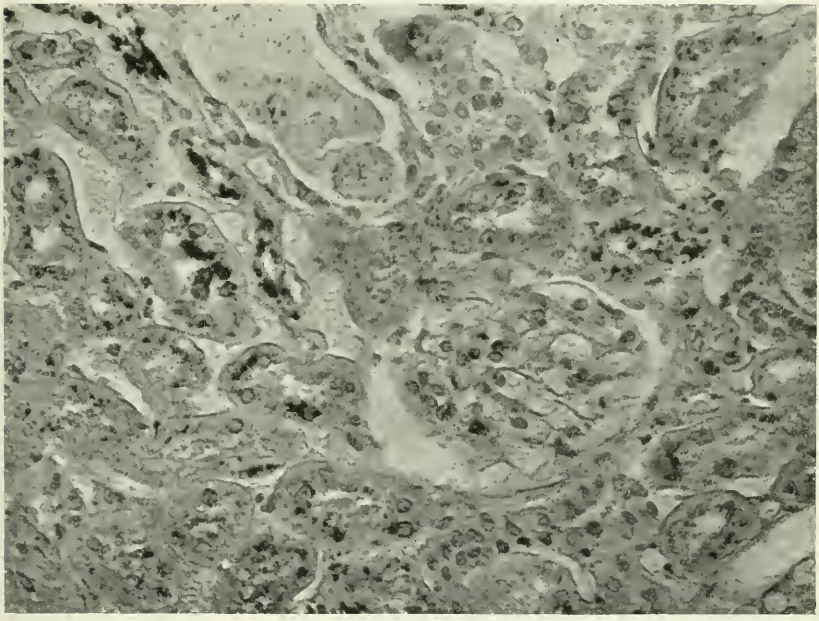

FIG. 4.—Kidney of a rabbit (B) transfused 120 times in the course of 180 days. The glomeruli are free from pigment, but it is present in all the tubules except the collecting ones, being especially abundant in the ascending limb of Henle's loop and in the distal convolutions. A cast is to be seen containing many fine hemosiderin granules.

Kidneys. There was in the rabbits a marked siderosis of the kidney parenchyma (Fig. 4) somewhat more general in its distribution than is the case in human hemochromatosis. In this latter disease the pigment is, as a rule, sharply localized to the ascending limb of Henle's loop and to the distal convoluted tubules, where it is abundant; while the rest of the parenchyma, save in some

cases the glomeruli, is free from it. Gaskell and his associates[9] point out that in pernicious anemia, by contrast, the pigment is found almost wholly in the proximal convoluted tubules. In our rabbits the glomeruli never showed pigment, but the cells of nearly all the cortical tubules contained it. Very fine granules were

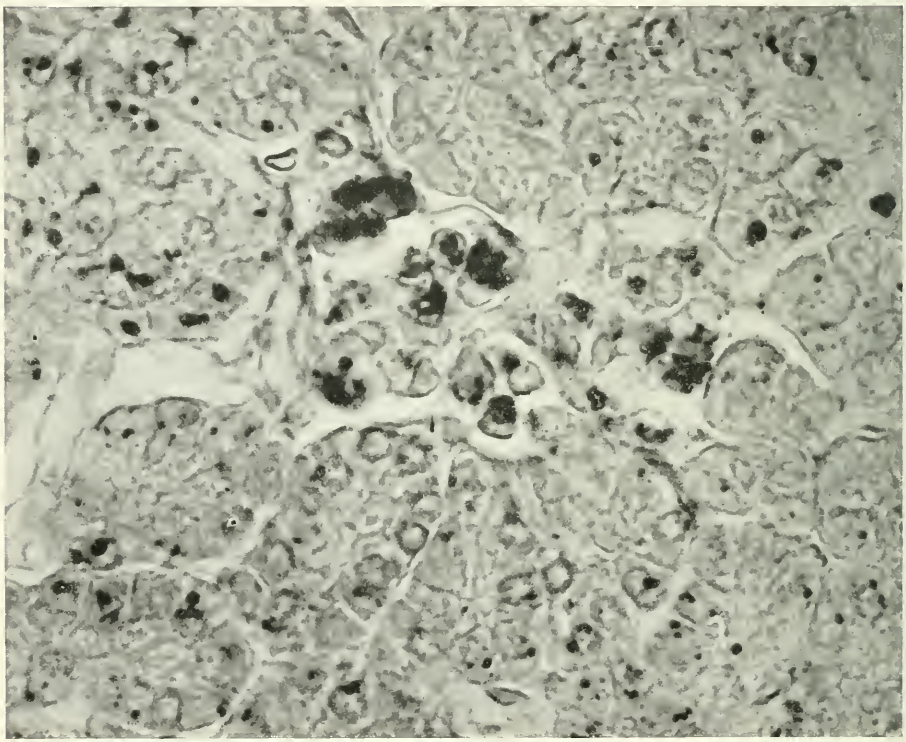

FIG. 5.—Pancreas of a rabbit (C) transfused 156 times in the course of 194 days. The alveolar cells toward the center of the photograph contain hemosiderin in especially large amount.

present in moderate number in the proximal convoluted tubules; more were to be seen in the descending limb of Henle's loop; and the ascending limb and distal convoluted tubules were very heavily pigmented with coarse, granular agglomerates, just as in the hemochromatosis of man. And, as in this disease, the collecting tubules and medulla were free from pigment.

Pancreas. Only in the animals transfused during a long period was this organ pigmented. Fine hemosiderin granules were then demonstrable in the alveolar cells, often in considerable quantity (Fig. 5). The islands of Langerhans were always normal, and there was an entire absence of the cirrhosis which in human beings may be marked. But there was an absence too of the destruction of gland tissue through excessive pigmentation which many authors hold to be the cause of the cirrhosis.

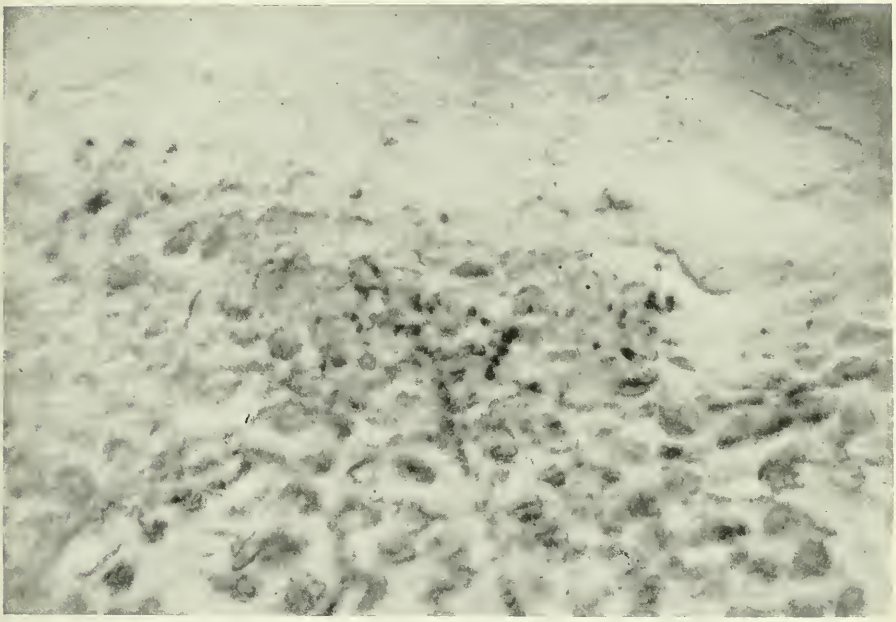

FIG. 6.—Iron-containing pigment in the peripheral cells of the zona glomerulosa of the adrenal gland. Rabbit C. The connective-tissue capsule of the organ occupies the upper part of the photograph.

Adrenals, Stomach and Intestines. In two rabbits the adrenal glands showed a slight siderosis and in precisely the region where pigmentation is found in man; namely, in the zona glomerulosa of the cortex (Fig. 6). The intestines, as in the human instance, were free from hemosiderin save for the granules in a few connective-tissue cells scattered throughout the coats. But the stomach also was unpigmented, whereas in the human stomach the glands of the

mucosa are usually the subject of an outspoken siderosis, especially at their base.

Heart. This organ showed pigment only in the rabbits that were transfused longest. The hemosiderin was deposited in fine granules throughout the muscle fibers, being especially abundant close to

FIG. 7.—Heart muscle of Rabbit A. The hemosiderin is especially abundant at either end of the nuclei of the muscle fibers.

either end of the nucleus (Fig. 7). An identical localization of the pigment is found in human beings; but the amount is, as a rule, far greater, sometimes leading to death of the muscle fibers with connective tissue overgrowth as a further result.

Lungs. Neither in man nor in the rabbit is there a noteworthy pigmentation of the lungs. A few iron-containing cells may be

present here and there in the reticulum and sometimes in the capillaries.

Lymph Nodes. In the rabbits with most advanced siderosis large masses of free iron-containing pigment were present in the sinuses of the lymph nodes draining the liver (Fig. 8) and granules were present in many cells as well. The other abdominal lymph nodes also contained iron in some quantity, but so sometimes do those of the normal rabbit. The mediastinal lymph glands of the

FIG. 8.—Section of a lymph gland draining the liver of Rabbit A. Large aggregates of extracellular hemosiderin are to be seen.

transfused rabbits and those from the groins and axillæ showed at most only a few granules. This localization of hemosiderin to the nodes draining heavily pigmented organs is the rule in human hemochromatosis.

Skin. The bronzed portions of the human skin usually contain slaty brown pigment granules in the basal layers of the epithelium, which do not react positively to the tests for iron. Ordinary hemosiderin is present as well in connective-tissue cells of the corium,

especially about the sweat glands. In our rabbits the epidermal pigment was lacking, but connective-tissue cells containing hemosiderin were often fairly numerous in the corium (Fig. 9).

Other Organs. In one of Sprunt's cases the tracheal cartilage was pigmented and in another the submaxillary gland. Both these lesions have been found in our rabbits. Siderosis of the submaxillary gland was well marked in one animal, the granules lying grouped

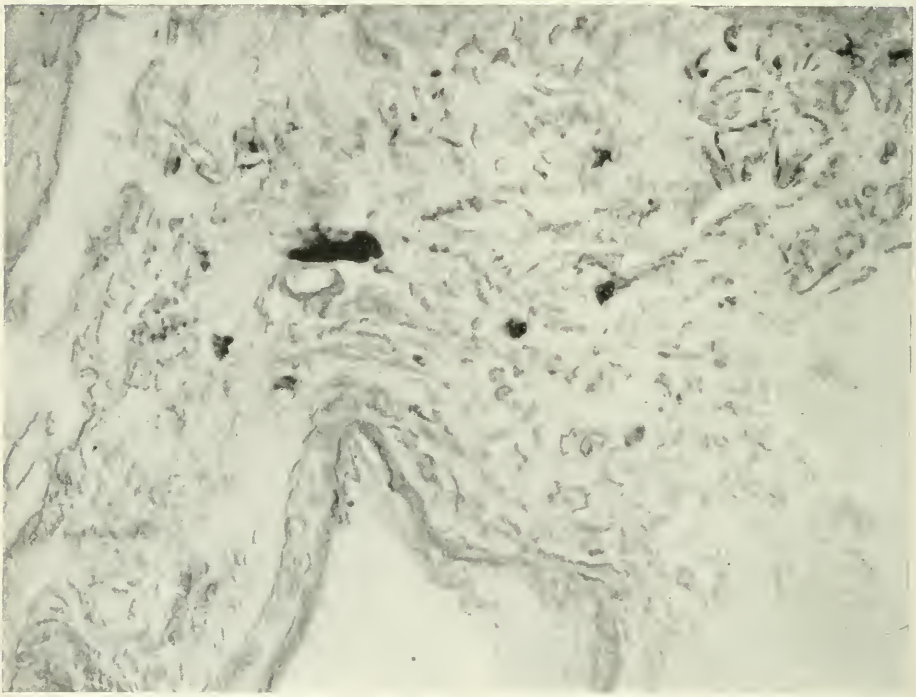

FIG. 9.—Skin from the abdomen of Rabbit B. Iron-containing pigment is present in scattered cells of the corium.

in the alveolar cells (Fig. 10). The rabbit thyroid, on the other hand, was never affected, whereas in man it may be loaded with pigment. The rabbits transfused longest happened to be old females. In them a pronounced siderosis of the mammary glands was regularly present, certain cells of the epithelium being distended with pigment, while still others containing it had desquamated and could be found free in the lumen of the ducts (Fig. 11). There is no parallel

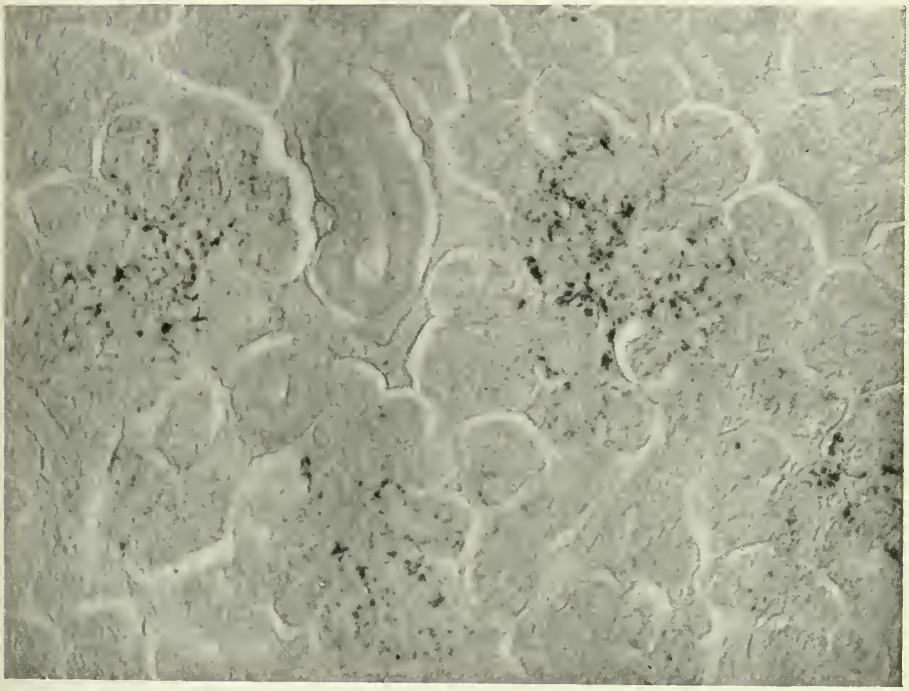

FIG. 10.—Hemosiderin granules in the alveolar cells of a submaxillary gland. Rabbit C. The patchy localization here seen was present throughout the gland.

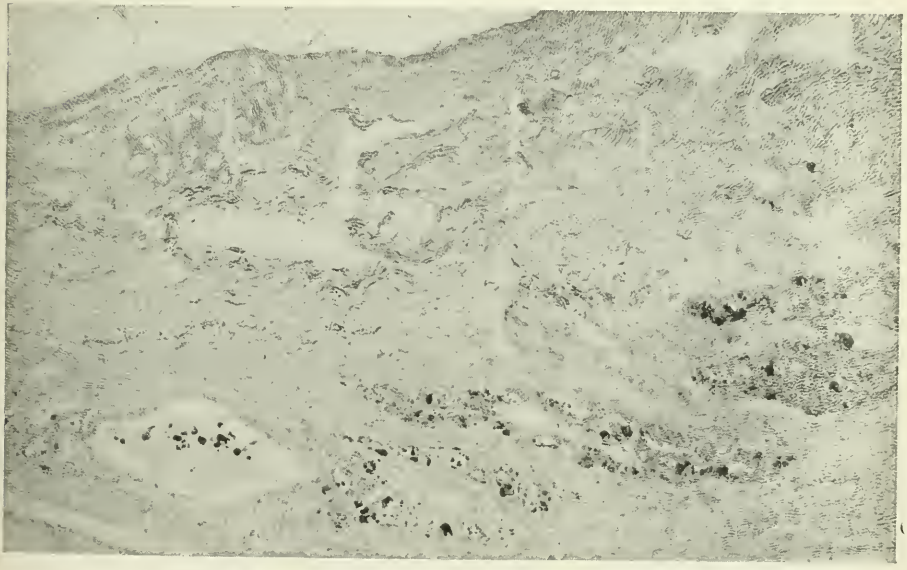

FIG. 11.—Mammary gland of Rabbit A, an old female. Many of the heavily pigmented cells have desquamated. The animal had not been pregnant during the period of transfusion.

in man for this lesion, since human hemochromatosis is a disease of the male. Abbott's description of the single case on record in a female does not include a report on the mammary glands.

Relation of Cirrhosis and Pigmentation. Hypertrophic cirrhosis of the liver is a constant feature of human hemochromatosis, but whether it is a primary or secondary factor in the disease has not been determined. There is no doubt that a fibrous overgrowth is often present that has been induced by parenchymal destruction. The evidence of such a secondary connective-tissue proliferation is so clearly visible in autopsy material that many authors have been led to consider the entire cirrhosis as secondary. But actually the recognition of areas of induced cirrhosis proves nothing either way, since they would be present in any event were the pigmentation sufficient to cause parenchymal destruction.

The transfused rabbits were killed at a relatively early stage of hepatic siderosis, and the ability of this latter to induce cirrhosis in the absence of cell destruction can be well judged from the findings. At the periphery of the lobules the parenchymal cells were heavily pigmented, but as yet only here and there had one broken down. Cirrhosis was practically absent, save for that of an intercurrent nature, which at most was slight, and obviously it had not followed the pigmentation, being often well marked where the latter was negligible. Here and there in the lobular capillaries were great masses of iron pigment, some of them as much as 80μ across, more or less completely enclosed in multinucleate giant cells. But though these pigment masses had induced pressure atrophy of the surrounding parenchymal cells, no connective-tissue reaction had taken place about them. It may be urged that proliferation might have ensued in time, and this is not impossible. Yet in view of the lack of an immediate reaction the conclusion seems justified that hemosiderin when enclosed in living cells has no noteworthy stimulative effect on connective tissue.

Hepatic changes similar in degree to those in the rabbits cannot be expected at the average human autopsy, since patients with hemochromatosis do not, as a rule, succumb to the disease until the pigmentation has destroyed large numbers of parenchymal cells with a resulting connective-tissue overgrowth. Only by some

chance may one expect to obtain the liver at an earlier stage. Such a chance has recently come to us in the case of hemochromatosis already mentioned. The patient died, not of this disease, which apparently had lasted about one and one-half years, but of an old chronic myocarditis.[11] The cells at the periphery of the liver lobules were pigmented only to the degree found in rabbits and showed no evidence of injury. But here the parallel ceases. For whereas in the rabbits an hepatic cirrhosis was absent, in the human liver a strikingly abundant one was found, interlobular and of long standing, as shown by its character. Save in the cells of the many new-formed bile ducts, the cirrhotic tissue contained almost no pigment. That the connective-tissue overgrowth was in this instance the result of parenchymal destruction from excessive pigmentation is out of the question. One is led inevitably to conclude that it must have been a primary feature of the patient's disease.

If the fact is granted, as the evidence warrants, that cirrhosis is a primary occurrence in some cases at least of hemochromatosis, this does not mean that it is without a relation to the characteristic pigmentation. Kretz[12] has shown that cirrhosis of any sort is frequently accompanied by a more or less marked siderosis of the liver. He found such a pigmentation in fourteen out of twenty-six cirrhotic livers, whereas in only one of every fifteen or twenty that were non-cirrhotic was it present. The rabbit material has furnished striking proof that when a tendency to siderosis exists an intercurrent cirrhosis will greatly increase the deposition of pigment. In one transfused animal with a very moderate general siderosis of the liver an adhesion had occurred connecting the anterior edge of a lobe with the abdominal wall and thus inducing a well-marked local cirrhosis. Here the liver cells were so heavily pigmented as in many instances to be scarcely recognizable and in others to have broken down (Fig 12). The contrast to the parenchyma elsewhere in the organ was extreme. In a second animal, as well, a local cirrhosis of unknown origin was accompanied by great local pigmentation. It is perhaps not a matter of accident that the rabbit with the most pigmented liver had not been transfused longest but was the subject of an intercurrent cirrhosis. In the

course of 167 days it had received 139 transfusions—52 of 10 c.c. each and the last 87 of 15 c.c. each. A companion animal of the same weight and sex, receiving in 194 days 156 transfusions, the last 99 of 15 c.c. each, had no cirrhosis of the liver and exhibited by contrast little pigmentation.

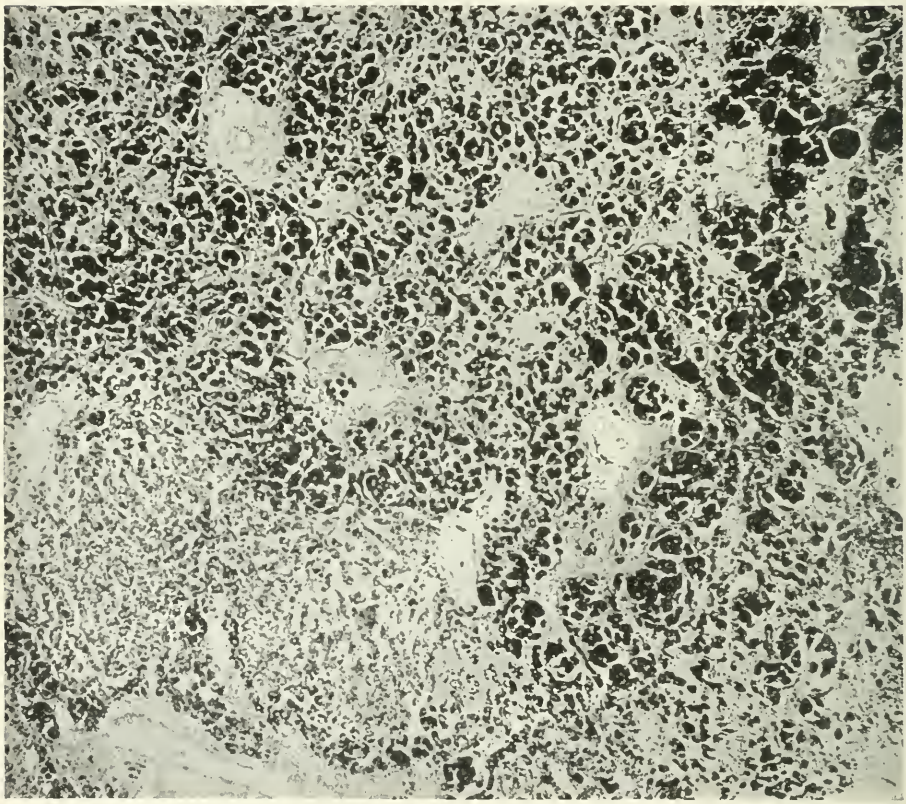

FIG. 12.—Heavy pigmentation secondary to a local cirrhosis of the liver. Rabbit B. Non-cirrhotic tissue may be seen at the lower left-hand corner of the photograph. Here the pigmentation of the parenchyma is by contrast very slight.

All this gives good reason for the supposition that the pigmentation of the liver cells in human hemochromatosis is in large part, if not entirely, secondary to the cirrhosis. Whether the connective tissue overgrowth of the pancreas that is so often observed is an essential phenomenon of the human disease or is secondary to the

abundant parenchymal destruction, our work does not enable us to say. But a similar fibrous overgrowth, which is obviously of secondary character, may often be observed in the heavily pigmented heart of hemochromatosis cases and sometimes in the thyroid gland.

Injury and Pigmentation. Signs of an old perirenal inflammation existed in one of the transfused rabbits, and in the scar tissue here numerous connective-tissue cells were noted containing hemosiderin. The observation led us to inject agar into the other animals of the series some days before killing them, with a view to determining whether iron would be laid down in the reactive tissue. Such was the case. The cells penetrating into the interior of the agar mass were unpigmented, which was to have been expected, since they were in process of rapid proliferation, but in the older reactive tissue hemosiderin was fairly abundant as small granules in the fibroblasts (Fig. 13). Its constant presence and general distribution rules out the possibility that it was derived from local hemorrhages.

A similar relation of injury to pigmentation was observed in the human instance of hemochromatosis already several times cited. The arteries showed scleroses here and there. In the sclerotic patches iron was sometimes encountered in quantity (Fig. 14), whereas in the healthy arterial wall it was entirely lacking. The ability of hepatic cirrhosis to induce pigmentation is, of course, only another example of the effect of injury, but of injury this time to an organ essentially concerned in the degradation of blood pigment.

A simple explanation now suggests itself for the curious distribution of the cutaneous pigmentation in human hemochromatosis. The face and neck to the collar line, and the backs of the hands are the surfaces which become most bronzed and are often the only ones affected. These are precisely the surfaces most subjected to light, wind and other injurious influences, such as may be supposed from the evidence just given to conduce to a deposition of pigment. There is, however, no gainsaying the fact that not every sort of injury can bring about cutaneous siderosis, else one would expect it on the soles of the feet, for example. But the data given by Kretz show that even in the liver the injury must be of a special sort if iron is to be laid down. He has pointed out that neither

the liver degenerations which result from phosphorus and arsenic poisoning, nor chronic passive congestion, nor cholelithiasis with jaundice suffices to cause the least hepatic siderosis.

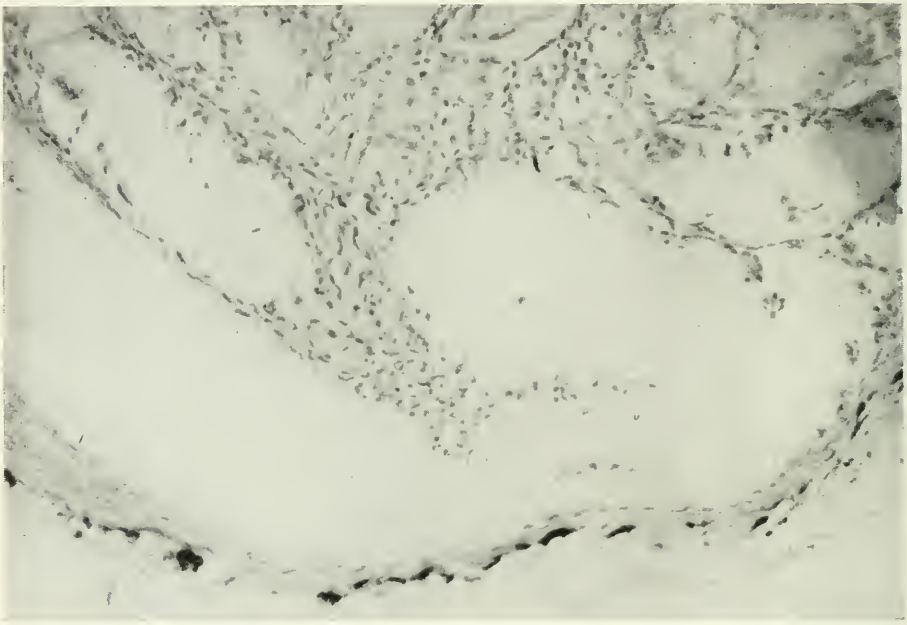

FIG. 13.—Hemosiderin in cells of the reactive tissue surrounding a mass of agar-agar. Rabbit B. The clear material is the agar, which is in process of organization. Iron-containing pigment is present only in the older scar tissue, not where the cells are actively proliferating.

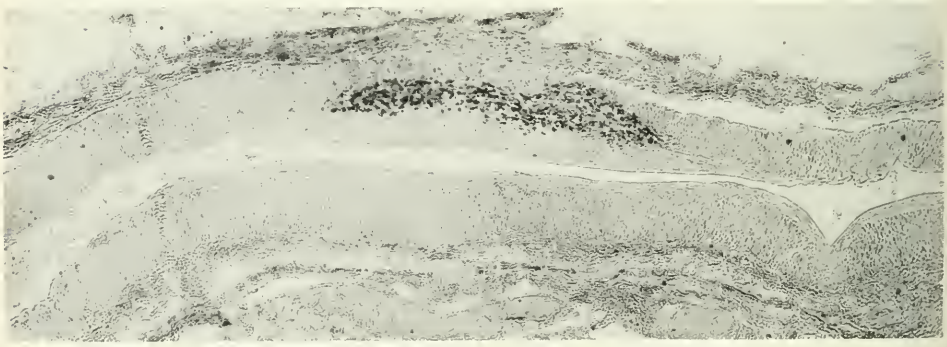

FIG. 14.—Sagittal section of a small artery from the patient with hemochromatosis. Iron-containing pigment has been deposited where the media is degenerated. The rest of the vessel wall is free from it.

An Aid to Diagnosis. Hemosiderin granules were frequently found lying free in the lumen of the kidney tubules of the heavily pigmented rabbits, and they were also noted embedded in casts (Fig. 4). The fact suggests that in human beings a diagnosis might be made through the demonstration of hemosiderin granules in the urine. This would be far preferable to the excision of a piece of skin, the procedure usual at present. A diagnosis has been accomplished by the method, as is shown in another paper.[10]

On the Sequence of Events in Human Hemochromatosis. The hemochromatosis of transfused rabbits, as thus far studied, has points of difference from the human disease, but also important points in common with it. The points of difference are in large part those of degree and of time. For instance, none of the animals developed diabetes; but for that matter in none was the pancreas greatly damaged as it is in *diabète bronzé*. The pigmentation of the pancreas, so far as it went, was like that occurring in man. This example well illustrates the general variances and likenesses found. The pigmentation of the rabbits was strikingly similar to that in human beings, not merely in kind but in distribution to the organs and in them. The sole difference in the pathological findings which must be considered as essential was the total absence in rabbits of the hepatic cirrhosis which in man is a constant and pronounced feature of hemochromatosis. There are good reasons, already stated, for the belief that this cirrhosis is a primary factor in the disease.

Most of the recent evidence in the literature is against the older view of excessive blood destruction in an otherwise healthy organism as the cause of hemochromatosis. So too are our experiments with rabbits. The transfused animals had disposed of immense quantities of blood before any noteworthy pigmentation appeared. Some of them received in the course of each week during a long period an amount of blood almost as great as their own original total quantity (5.5 per cent. of the body weight).[13] The organism was required to dispose of this and of its own wornout corpuscles as well, yet at most the pigmentation was moderate compared with that found in man. Needless to say this excessive and continued blood destruction could not be supported by the human body

without notable changes in the circulating red cells and the blood-forming organs, and these are completely absent.

While an increased destruction of red cells cannot be the primary cause of hemochromatosis, yet certainly one need look no further than these elements for the source of the hemosiderin. The presence of the pigment in such peculiar situations as the heart muscle and the parenchyma of many glands has led some authors to suppose that there must be a derangement of these tissues, causing them to elaborate hemosiderin out of their own proper substance. But in our rabbits the pigment laid down was manifestly attributable to erythrocytes undergoing destruction, and it was found in precisely the same situations as in human hemochromatosis.

The activity of the liver is known to be profoundly important to the working over of blood pigment. The sequence of events in human hemochromatosis would seem to be the following: A liver cirrhosis of unknown origin leads to a failure of the organ to deal adequately with the iron-containing products of normal blood destruction, and the latter accumulate in the organism. Widespread pigmentation results automatically. It at length becomes so great as to cause the death of parenchymal cells, especially in the liver and pancreas, thus leading to secondary connective-tissue overgrowth. This, in turn, through injury to the remaining parenchyma, hastens the accumulation of pigment. By a repetition of the vicious circle what is essentially a chronic disease becomes at length a rapid progress down hill. Diabetes appears in many cases as a result of the pancreatic injury, and death soon results. There is no link in this chain of events for which the facts do not afford strong evidence.

Summary. In rabbits destroying transfused blood constantly during a period of many months a pronounced and widespread siderosis ensues, practically identical with that characterizing human hemochromatosis. The findings do not indicate the ultimate cause of this disease, but they throw light on its various features and its course, and suggest a means for its diagnosis.

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THE INTRAVENOUS SERUM TREATMENT OF EPIDEMIC CEREBROSPINAL MENINGITIS

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NEW YORK

Base hospitals in the larger cantonments offer unparalleled opportunity for the study of the early stages of acute disease in large volume. Important clinical research, not of an academic peace time sort but of a practical kind which may assist in making and keeping men fit for military duty, may be carried out. During the past year at Camp Jackson we have devoted much time and thought to epidemic cerebrospinal meningitis. Through the coöperation of the division surgeon and his assistants among the regiments we have been enabled to study this important camp disease in its very earliest stages. As a result of this study certain opinions have been formed, opinions which we believe are of value in epidemiology, diagnosis and treatment.

As a result of a clinical experience with about 240 cases, we believe that the disease is in most if not in all cases a general blood-stream infection—a sepsis—with secondary meningeal involvement. About 45 per cent. of our cases have been recognized in what may be called the premeningitic stage, the stage in which the spinal fluid is clear and in which the symptoms are largely those of a generalized disease. The average duration of this stage is forty-eight hours. In some cases it is ill-defined, but in a very large proportion may be recognized. About 4 per cent. of our cases of meningococcus infection have not developed meningitis. In the fulminating cases death often ensues from overwhelming systemic disturbance without any clinical or gross necropsy evidence of meningeal inflammation. In the abortive cases meningitis may not develop. We have observed

a very few cases of generalized meningococcus infection with positive blood culture and metastatic inflammatory foci in the joints, accessory sinuses of the nose or middle ear altogether, without symptoms or signs of meningitis. At the present time there is in the base hospital, Camp Jackson, a soldier who after three weeks of irregular fever, with chills, a maculopapular rash and a blood culture positive for meningococcus, developed severe meningitis two weeks after organisms were found in the blood. These are further examples of "tardy meningitis," as recently described by H. Aime and H. Chene in the *Paris Médical* of February 8, 1918,[1] and lend added evidence to the view that the meningococcus is a general blood-stream invader in perhaps a larger number of cases than has been thought heretofore.

The positive blood culture in one-third of our cases of meningitis in which this has been carefully made, the widespread character of the complications, such as panophthalmitis, pneumonia, pleuritis, arthritis, pericarditis, endocarditis, with the recovery of the meningococcus from these regions; the frequent petechial rash; the well-marked premeningitic stage in the more typical cases; the response to large doses of serum intravenously, all tend to confirm the belief that meningococcic meningitis is frequently if not always a primary sepsis. Detailed argument might be given on each of these points with citation of cases, but for this there is not time. The point of view expressed has of late also been developed by certain European observers, notably Netter[2] and Thomsen and Wulff.[3]

The clinical aspect of the early stages of meningococcus infections has been described in an article in the *Archives of Internal Medicine* for April, 1918.[4]

Fifty-five per cent. of our cases have entered the hospital with meningitis present. It is of interest that cases coming with fully developed meningitis ordinarily give a history of a longer period of illness than those admitted with clear spinal fluid.

To treat as a mere local process a disease that so frequently presents itself as a sepsis seems to deny the repeated clinical observations made in our receiving ward. Acting, therefore, upon an opinion formed as a result of the study of the first 50 cases of the epidemic, we began to supplement the former method of intraspinal treatment by intravenous serum therapy in an attempt to meet the blood-

stream infection, if possible, before secondary meningeal localization had taken place. This was done timidly at first, using small doses, and then only in cases responding unsatisfactorily to the older intraspinal treatment. This partly explains the high mortality in the cases receiving small doses of serum intravenously early in the epidemic.

As success increased when the larger doses were used, boldness increased. For much of this courage in the intravenous use of large amounts of serum we are indebted to the studies of the Rockefeller Institute in the serum treatment of pneumonia.

Of our 240 cases, 92 were treated by the intraspinal method alone, the remainder by combined intravenous and intraspinal treatment. About 60 cases have been treated by the fully developed method to be described; 50 consecutive cases are summarized. These were soldiers admitted to the base hospital between January 20 and April 15, 1918. Bacteriological findings were positive in all but 3 cases; in these 3 clinical evidence was unquestionable. Abortive cases without bacteriological proof are not included.

I would not for a moment seek to convey the impression that the treatment to be advised may relegate to a position of secondary importance the intraspinal methods that have been recommended by Dr. Flexner and others. We have used the intraspinal method thoroughly and consistently in almost every case and believe that to this fact is due much of the success in reducing mortality. In ordinary civil hospital or family practice it is probable that diagnosis in the stage of sepsis will be infrequent and that under such circumstances direct treatment of the disease process when it has localized in the meninges will continue to be of primary importance. In military hospitals, however, where material can be controlled, where laboratory facilities are at hand and with trained personnel, diagnosis in the premeningitic stage should be possible in many cases. It is here that intravenous serum therapy gives the happiest results.

The method of treatment used in the 50 cases to be summarized is as follows: As soon as possible after admission a desensitizing dose of 1 c.c. of serum is given. The intradermal test to determine sensitization has not been found necessary as a routine. One-half

hour later morphin, $\frac{1}{6}$ grain, and atropin, $\frac{1}{100}$ grain, are given hypodermically. One hour after the desensitizing dose of serum the first intravenous injection is given. The amount of this injection is 60 to 150 c.c., and is graduated somewhat according to the patient's weight and the severity of the symptoms. The serum is undiluted. Following the work of the Rockefeller Institute in pneumonia we have found that the secret of safe serum administration is the slow injection of the first portion of the dose. Our ward rule is that the first 15 c.c. shall be injected at the rate of 1 c.c. per minute. Dyspnea, cyanosis, pallor, vomiting, weak and irregular pulse or other signs of immediate serum effects are a signal for the cessation of treatment. In such instances the attempt to introduce the serum is renewed in two hours when it rarely fails.

In no case has there been failure to give all the serum the patient's condition appeared to demand. No serious symptoms have resulted with the precautions described, although the late serum effects have often been severe. The flow of the serum is accurately controlled by giving it in large glass syringes. The intravenous injection is repeated every eight to twelve hours in the serious cases until the temperature becomes normal and the symptoms seem under control. Among the 50 cases to be summarized the average number of intravenous injections was 4.5; the highest number in any one case was 10 and the lowest 1. The average amount of serum given by vein was 285 c.c., the largest was 705 c.c., and the smallest 50 c.c.

The Intraspinal Treatment. In the stage of clear spinal fluid without cellular increase, with or without a trace of globulin and with the presence of isolated microörganisms, we have, as a rule, not used the intraspinal injections, deferring them until actual meningitis has developed. We have been somewhat influenced in this by Amoss's work in poliomyelitis, which has shown the increased permeability of the choroid plexus as a result of such injections. Experience with intraspinal serum treatment emphasizes also the fact that serum is in itself an irritant and produces a certain amount of inflammatory reaction in the meninges. It is possible we have erred in not injecting serum generally in this stage, but present clinical results seem to justify this plan. Opinion about it is subject to revision through added experience.

Lumbar puncture is repeated at intervals of six to twelve hours after the diagnosis has been made and intravenous treatment started. When the cell count has risen and the spinal fluid has become cloudy the usual intraspinal treatment is begun. We have relied greatly upon free drainage and have performed this about one-half hour after the intravenous injection. As the choroid plexus is permeable by reason of the inflammation, drainage at this time may increase the amount of antibody which should find its way from the blood into the upper cerebrospinal spaces. In connection with this point the recent work of McClendon[5] on the spinal fluid as an ultrafiltrate is of interest. In the severe cases with active meningitis we have drained twice in twenty-four hours, removing sufficient spinal fluid to reduce the pressure to an approximate normal and have introduced rarely more than 20 to 30 c.c. of serum. The average number of spinal punctures in these 50 cases was 6, the average number of intraspinal serum injections 4. The highest number of lumbar punctures in any one case was 15 and the lowest 2. The average total amount of spinal fluid withdrawn from any patient was 280 c.c., the largest amount was 835 c.c. and the smallest 70 c.c.

We have not been inclined nor have we found it necessary in the present method of treatment to continue the intraspinal injections beyond the first five or six days. As has been noted by other observers the symptoms of meningeal irritation are often increased by too many injections. When there is bitter complaint of the treatment and severe headache and pains in the back and lower extremities follow it we have relied upon free drainage and intravenous injections. It is sometimes better judgment to refrain from all treatment even when organisms persist in the spinal fluid. It is astonishing how quickly some of these cases will clear up when left alone.

Effect of Combined Treatment. As a rule the temperature becomes normal or subnormal in forty-eight hours after beginning the treatment, but rarely remains so. Usually there are oscillations to 100 degrees or more for the next two or three days. Fever may continue and merge with that of the serum sickness which follows a week or more after onset. The change in the patients, however, is

generally remarkable. The unconscious patients arouse and become rational; the petechial rash which has been such a prominent feature of the epidemic ceases to extend and rapidly fades and the dusky pallor is replaced by a more normal color. From a state of complete prostration the patient in a surprisingly short time is rational, hopeful and apparently out of danger. Usually the organisms disappear from the spinal fluid at this time and the other evidences of inflammation in the spinal canal clear up. Lumbar puncture is continued at intervals of twenty-four to forty-eight hours until the process is more or less complete. This transformation from desperate illness to comfort and comparative safety is perhaps the strongest argument for the method of treatment described. It must be observed to be understood. While this happy result is the rule there are a few cases that have not so responded. In most of these we have not given continuous intravenous treatment but have allowed an interval to elapse, usually forty-eight hours, and have then with serum from another source given a second series of intravenous injections. In these cases spinal drainage and intraspinal serum administration is carefully carried out because of the ever-present danger of blocking of foramina and consequent hydrocephalus. This intermittent intravenous therapy is based upon nothing except the results of clinical study and is therefore subject to all the errors of such observations. Longer experience may prove judgment in this matter erroneous. In infants and small children in whom intravenous injections have been difficult the serum has been administered subcutaneously with apparent satisfactory effect.

Results of Treatment. In discussing the results of the method of treatment described it may be said that we had to deal with a virulent type of meningococcus. At the meeting of the South Carolina State Medical Association, April 17, Dr. Hayne, State Health Officer, reported 108 cases among the civilian population throughout the State; 43 of this number had died and 27 had recovered. Result was unknown in the remaining 38. The mortality was surely 40 per cent., probably higher. In some communities (as Newberry, S. C.) the mortality among small groups of cases was 90 per cent. Our numerous fulminating cases with speedy death bore testimony to the virulence of the disease. I should add that of

the 50 cases summarized 10 were blacks. In none of these was it possible to make a diagnosis in the premeningitic stage. In the average Southern negro a diagnosis depending upon a rash, somewhat subtile changes in attitude, manner, facies and reflex irritability along with an accurate history is a baffling task. This feature of the later stage of our work in meningitis has been somewhat discouraging. Twenty-one of these 50 cases were recognized before the spinal fluid became cloudy; in 29 the diagnosis was late. Of the 21 diagnosed in the early stage 19 lived and 2 died. Of the 29 recognized later 5 died. The total mortality in these cases was therefore 14 per cent. Twenty per cent. of the blacks died and 12.5 per cent. of the whites. Of the 6 who died, 1 came to the meningitis ward in the acute stage of measles with severe bronchopneumonia, during which he developed a terminal meningitis; 3 others died from pneumonia, making 4 deaths with this complication; 1 died from blocking of the foramina and hydrocephalus; 1, a negro, came to the hospital in the late stages of the disease and died shortly after admission; 1 had gangrene of the toes of both feet from an apparent acute trophic disturbance with blocking of foramina. All the others are either returned to duty or are up and about unquestionably convalescent. In judging the clinical results of the treatment of meningitis it is necessary to take account of the complications, since these have such important bearing on the future of those who survive; 7 of the 50 cases tabulated had either lobar or bronchopneumonia—an astonishingly high percentage; 3 had arthritis or about the ordinary percentage of the entire epidemic; 2 had orchitis; 1 had gangrene of the toes; 2 had blocking of the foramina. Aside from these there were no serious after-effects. None of the series had panophthalmitis, no survivor paresis, deafness or other permanently disabling sequel. The percentage of such complications in cases treated by former methods are higher—panophthalmitis, for example, was present in 5.4 per cent., and deafness in 4 per cent. It is our opinion that where the clinical material can be controlled, where men expert in the recognition of the early stages of meningococcus infections are at hand and a laboratory available the mortality should not exceed 15 per cent., and the disabling complications be fewer than has been the case heretofore.

Success in this as in all other things depends directly upon the care of details, upon a knowledge of when not to treat as well as when to treat.

Those of us who in a winter rich with experience in the care of acute disease in large volume have faced a grave epidemic of meningitis, feel that we shall in the future view this serious disease with greater equanimity, believing that in the conception of the disease as a primary sepsis, in an early diagnosis and in a combined intensive intravenous and intraspinous serotherapy lies the secret of reducing mortality to a figure below the expectancy of many other serious acute infections.

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DISCUSSION

Dr. Wadsworth said: In view of the variation in therapeutic action of the different antimeningococcus serums and the lack of potency in some of the commercial serums, it is essential that the clinician who uses the serum should know its character and potency as determined by either specific complement-fixing properties or the agglutinating action against the different types of the organism. Hitherto the only complete statistics are those of the Rockefeller Institute, where reports of the therapeutic results are received from all cases in which their serum has been used.

Dr. Amoss reported the results of tests which he made of commercial serums, but with only five selected strains. We have carried out similar tests with all of the fifty-one strains which we used in producing our serum. In general, the conclusions from these tests—that the commercial serums at the time of testing, 1917, were not reliable—confirm one with the other. Recent tests of two of the commercial serums indicate that the manufacturers are now producing satisfactory serum, but the potency of

the serum has not been recorded on the label. This is now required by regulation in the State of New York. The Public Health Council, at the suggestion of the Commissioner of Health, Dr. Biggs, passed a regulation to this effect in the Sanitary Code of the State which has the force of law. Thus a beginning has been made which ought to be helpful to clinicians in their study of the serum therapy of the disease and provide a more satisfactory basis for accurate statistics.

THE RAT AND INFANTILE PARALYSIS—A THEORY

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Second Communication[1]

In a paper published in the *Boston Medical and Surgical Journal* for September, 1916, I discussed the epidemiology of infantile paralysis from two standpoints, presenting, in the first instance, evidence against human contact, direct or indirect, as being the determining factor in the spread of this disease, and, in the second place, suggesting that the epidemiological facts could be better harmonized if one assumed an antecedent and underlying infection of rodents, and the mediation of the flea.

I have been told that my argument against the role of human contact was much stronger than that in favor of the rat. The justice of this criticism I acknowledge freely.

Manifestly, the truth or falsity of the rat theory must, in the end, be proved by laboratory investigations which are still almost entirely lacking. Is the rat susceptible to the virus of infantile paralysis? As used by Flexner and others the virus has not produced characteristic disease in rats. On the other hand, as used by Rosenow and his co-workers, almost all the laboratory animals have been found susceptible to infection. If guinea-pigs can be infected easily, it is highly probable that the same will be found true of rats. Personally, I have not been able to undertake this laboratory work.

My purpose in this present paper is to strengthen, by additional epidemiological data alone, my hypothesis that a rodent epizoötic must and does precede human infantile paralysis.

Before taking up the question of rodents, however, and their possible relation to the disease, I will offer some further evidence that, in the transfer of infantile paralysis, human beings are not themselves of importance, directly or indirectly, as far as infectious secretions or excretions are concerned, though, as we shall see later, healthy third persons, as carriers of *infected fleas*, may be of very great importance. This new evidence has been furnished in great part by Prof. Charles T. Brues,[2] who, as consulting entomologist, investigated the New York City epidemic of 1916, and who, under urban, and, therefore, as generally considered unfavorable conditions, was, nevertheless, able to develop epidemiological facts of apparently great importance. For instance, whoever has seen a city slum street in summer-time cannot imagine more intimate personal contact than is enjoyed by the tenement children playing in the crowded, hot, dusty thoroughfare, and yet it appeared that cases of infantile paralysis might be numerous in the tenements on one side of a street, with no cases whatever in similar houses opposite. (See Chart I.)

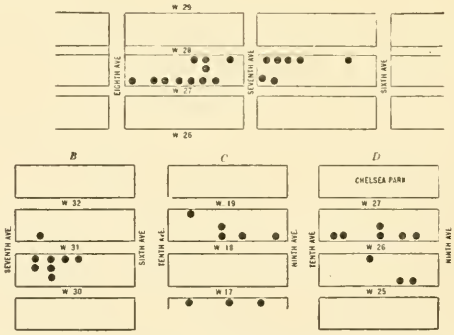


Chart 1.—Four groups of cases of poliomyelitis on the west side of Manhattan, illustrating the typical group of cases. Each dot represents one case; those along the street show the approximate position of the house and those away from the street, additional cases in the same house. New York City Report, 1916.

The contagium appeared, therefore, to be quite sharply localized in the quadrangle formed by the tenements bounding a city block, and did not travel across the street in spite of all the human migrations and opportunities for direct and indirect contact. If human carriers could not carry the infection across the street, then it is

equally improbable that the cases in the same block were transferred one to the other by human agency. On the other hand the unrestricted migration of infected rats over the back yards enclosed by such tenement quadrangles would explain quite adequately the sharp localization of the human cases. A somewhat parallel phenomenon has been seen in plague conditions in India, where people of different castes never associate with each other. In spite of this absence of human contact, plague spreads from caste to caste. The explanation is, in the end, simple: although personal association is forbidden, the houses, fronting oftentimes on different streets, have adjacent back yards over which rats travel freely.

In this connection it may be noted that in India the distribution of rats has been found to be very irregular. The general character of a building is no index to its rat population. In a considerable collection of old ramshackle buildings, perhaps only one or two will be found to be rat-infested. On the other hand, buildings apparently well-built and well-kept, and occupied by the well-to-do class, are not infrequently overrun with rats.

A study of secondary cases by Professor Brues showed, furthermore, that a large percentage occurred in other families of the same building with little or no personal contact, whereas in scarlet fever and diphtheria most of the secondary cases occurred in the same family. (See Table I.)

Table I.—Localization of Secondary Cases

	Cases in same family, per cent.	Cases in same house but different family, per cent.
Poliomyelitis	335 or 56	257 or 43
Scarlet fever	198 or 86	31 or 13
Diphtheria	73 or 78	20 or 21

I shall have occasion to refer again to Professor Brues's work, but it may be said here that conditions, as he found them, argued strongly against human contagiousness, and suggested as strongly an underlying animal reservoir of infection with an intermediary insect host. If the latter surmise be true then no combination satisfies the world-wide and the peculiar seasonal incidence of infantile paralysis but the rat and the flea. Such a theory would

not, of course, exclude the occasional involvement of other rodents or even other animals not of the rodent family.

Having brought the rat and flea under strong suspicion, it was but natural that a comparative study of infantile paralysis and bubonic plague should next be made, and to me, at least, the points of resemblance of these two diseases are quite remarkable.

That the rat and the disease are in some way associated has been known many centuries: witness the old coin with the image of Apollo, the god of pestilence, upon it and at the god's feet a rat. Nevertheless, it was but a few years ago that the contagiousness of bubonic plague was strongly urged even though, as in infantile paralysis, the spread of the disease in hospitals was practically unknown. Indeed, it was frequently remarked that, during a plague epidemic, the safest place was the plague hospital. Concerning infantile paralysis, Health Commissioner Emerson made a quite similar observation, that apparently the safest place in New York for a child was a children's institution, where the disease was rare, and, if introduced, did not spread. Ninety-five institutions held 29,000 children, but only 12 cases involving 6 institutions occurred.

Note, furthermore, is to be made of the fact that during an outbreak of poliomyelitis in Burlington, Vt., an orphan asylum in the middle of the infected district had no cases. The failure of infantile paralysis to spread in hospitals, schools, and institutions has its complete parallel in bubonic plague. A case of the latter disease imported into an uninfected locality never spreads. (That is to say, unless infected fleas are imported at the same time. The rare instances in which infantile paralysis is seen in hospitals or children's institutions may well be due either to the limited occurrence of rodents in such institutions, or to the importation of infected fleas, from the outside either by visitors, new inmates or institutional employees.) Stephens[3] in Australia noted that whereas cases of infantile paralysis did not spread in the general hospital wards, this could not be said of the out-patient departments in which occurred marked and indiscriminate mingling of all sorts of people. It is not difficult to imagine the introduction into such out-door departments of infected fleas or other insects.

In this connection it is interesting to quote from the New York City Report of 1916 that "no attendant, physician, nurse or domestic, and no patient admitted to any of the hospitals throughout the State, for other cause than poliomyelitis, during the epidemic, contracted poliomyelitis. . . . One of the field nurses of the department engaged in daily house-to-house visits among the families where active cases were isolated, developed poliomyelitis in a severe paralytic form." The fact that the hospital personnel in infantile paralysis does not acquire infection is an experience so nearly universal that the rare exceptions serve only to prove the rule. In other so-called contagious diseases such as diphtheria, scarlet fever, and even typhoid fever, ward infection of nurses and other attendants is very common. It can be said, therefore, of infantile paralysis with almost absolute certainty that the virus, as present in such hospital wards, must be in an inactive state. The same can be said also of the virus as used by laboratory workers, for no case has come to my notice in all the literature in which a laboratory worker has acquired infantile paralysis in the course of his investigations, even though, as in one instance, the syringe broke and virus was sprayed into the face of the investigator. From the New York Report, however, we note that a nurse engaged in a house-to-house visiting of cases acquired the disease and other similar instances in doctors and nurses are on record. In other words, people who visit infected districts, be they children or adults, doctors, nurses, or laymen, meet the virus apparently in a very active state. This sharply activating influence, not seen in hospitals, schools, or institutions, but present in the homes and quite definitely limited by seasonal influences, lies almost certainly in some insect, most probably the flea. Whether or not a secondary cycle of development, limited in time, takes place in the insect can be determined only by future investigations. There is considerable evidence, however, that the period of infectivity in any particular locality is quite sharply limited.

Bubonic plague in human beings is always preceded by rat plague, and in nearly all, *though not all*, epidemics sick and dead rats are in evidence and give the alarm. In Liverpool, for instance, three cases of human plague occurred, but no plague rat was ever found,

though diligent search was made. Furthermore, for every plague rat that is seen, hundreds die unseen. The fact, therefore, that sick or dead rats are rarely seen during epidemics of infantile paralysis is no evidence that rodent infection does not occur.

Is there any evidence that during epidemics of infantile paralysis rats are sick or paralyzed? Not much, but enough to suggest that we can find much more evidence if we look for it in a proper manner.

In 1909, my friend, Dr. J. L. Goodale, moved an old barn on his summer estate. Shortly after this, one of his sons and several other children of the neighborhood had infantile paralysis. At this time, Dr. Goodale on several occasions saw in his back yard rats, paralyzed in their hind-legs and able to move with difficulty. At the same time a cat became paralyzed on a neighboring estate.

In 1916 Mr. E. H. Williams, sent by me to investigate an epidemic of infantile paralysis in a certain New England town, saw, on the opposite bank of a small river running through the town, a rat hardly able to get over the rocks, because, apparently, of paralysis of the hind-legs.

Dr. W. H. Coon, in 1916, investigating for me infantile paralysis in a nearby town, found one case in which a child, a few days before infantile paralysis, played with a dead rat.

Dr. John Hitchcock tells me of a boy who, on waking in the morning, found a dead rat in his bed. Ten days later he came down with infantile paralysis.

Dr. John A. Ceconi, medical inspector for the Boston Board of Health, noted that in 1916 certain cases were coincident with excavating work on nearby streets and with the appearance of an unusual number of rodents. Ceconi further observed that five cases, grouped, four in one house and one in another next door, appeared after children from each household had played with a dead rat. Similar rat stories are, of course, common in plague epidemics. This latter group is especially interesting and important from several points of view: In the first place, the neighborhood had been free from infantile paralysis for six years at least. In the second place, there were no other cases in 1916 for many blocks around. The disease was, therefore, very sharply localized in the families of two adjoining houses. The parallelism with the bubonic

plague lies in the fact that the children played with a dead rat, and secondly, that in bubonic plague, dead rats are much more apt to be found in those localities in which multiple human cases occur in a family or in a house.

Epidemic Disease in Rabbits. Very recently I have learned that rabbits, more especially of the cotton-tail variety, are subject to periodic epidemic disease. The exact nature of this disease I have been unable to learn. The epidemics are said to occur at periods of six to ten years and the mortality is very high. The last epidemic occurred in 1916, the year when poliomyelitis was at its worst in the eastern United States. In this connection, it is interesting to note that the previous severe epidemic of infantile paralysis in Massachusetts was in 1910, an interval of six years. In Sweden, two large epidemics were separated by six years, 1905–1911.

In Australia, Altman[4] noted that infantile paralysis coincided in time with a public drive for the killing of rabbits with phosphorus. The point is, of course, obvious. Rodents dead from whatever cause mean the presence of a host of loose and hungry fleas. If these fleas harbor disease-producing organisms, they may transfer them to their human victims.

In a certain Massachusetts town in 1916 the only case of infantile paralysis to occur was in a young girl who lived 200 feet from a house in which a rabbit became paralyzed and died.

Pandemic Spread of both Diseases. Up to 1890, bubonic plague had been restricted to certain well-defined areas of Asia, but during the last twenty-five years, this disease has spread over the whole world. Within the same period of time, infantile paralysis, which previously had been noted in single small epidemics, has become world-wide in its distribution, with outbreaks much more numerous and of much larger size. (See Charts 2 and 3.)

Relation to Grain Traffic, Grist Mills, etc. This recent spread of plague I would ascribe to the marked increase in the world traffic in grain, for no fact is better established than the intimate relation of bubonic plague to the grain business. How about infantile paralysis? Wickman mentions three instances in which a localized outbreak began apparently at "the mill." The reason for this, in Wickman's opinion, was that the mill was the

place where neighbors came most into personal contact. The mill, however, is manifestly the place where human beings may be exposed to a maximum of rat and flea influence.

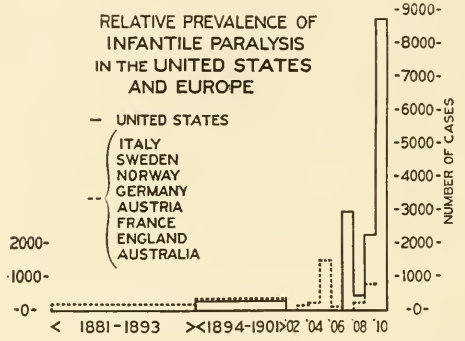


Chart 2.—From Report of Massachusetts State Board of Health, 1910.

Conway[5] at Hornellsville, N. Y., thought the outbreak due possibly to cat infection. Nearly all his cases, however, were connected directly or indirectly with a grain mill.

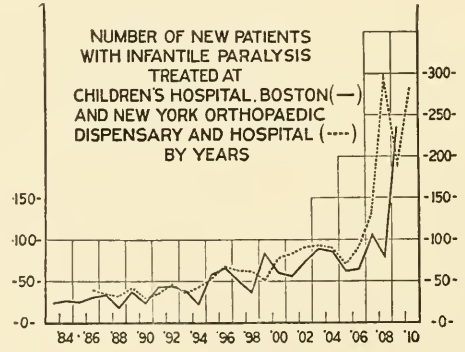


Chart 3.—From Report of Massachusetts State Board of Health, 1910.

The epidemic in 1914 at Barton, Vt., began "near the railroad station and rather near the grist mills." The association of infantile paralysis with the railroads has been generally noted. Grain warehouses and elevators are nearly always on the railroads.

Plague follows the railroad and other routes of transportation. Shidler tells of nine young adults who belonged to a *threshing crew* and acquired infantile paralysis at the same time.

In bubonic plague the relation of the cases to grain and other food supplies is marked. In the New York epidemic of 1916, Brues noted a quite similar propinquity of cases to bakeries, meat shops, stables, etc.

Role of Healthy Third Persons in the Epidemic Spread of Infantile Paralysis. Pim called attention in an English epidemic of infantile paralysis to the fact that the fathers of several cases worked together in a meat shop, though their abodes were far apart. Stephens (*loc. cit.*) says that the fathers of two children worked side by side. The inference is that these adults carried infected fleas home to their children. In bubonic plague infected workshops, even cotton mills have been primary foci of the disease. In Massachusetts in a certain large cotton mill, two young girls alone from a large mill population had infantile paralysis. They lived in sections widely separated, but, before their regular employment, they were associated together in cleaning out the general offices of the mill, which were directly over a large river, the banks of which were infested with rats. The role of third persons in the spread of infantile paralysis may consist simply in the transfer over considerable distances of infected fleas, which fleas may infect human individuals directly, or may set up a preliminary rodent infection. Such transfer is not uncommon in bubonic plague and in infantile paralysis would offer an explanation at least as good as infected secretions of the mouth and nose in such third persons.

Possible Role of Cats, Dogs, and Other Domestic Animals as Healthy Carriers of Infected Fleas. The fact that infantile paralysis occasionally invaded the homes of the well-to-do has been used as an argument against rodent infection as preliminary to human cases. It is, however, well known that rats may be present in localities where they would least be expected. Furthermore, pet animals might perfectly well carry to the children infected fleas. In bubonic plague it has been found that although the rat flea prefers its natural host, it can, in the absence of such natural

host, be found on practically all domestic animals. Furthermore, the human flea, *Pulex irritans*, has been found upon rats, and can, on occasion, transfer bubonic plague from animal to animal.

Transfer of Infected Fleas in Old Clothes, Junk, and Merchandise of Various Kinds. Bubonic plague has been carried from one locality to another by fleas harbored in the clothes of a person who has died of the disease. In the old clothes business, therefore, as well as that dealing with waste material in general, it is highly probable that the exchange of fleas between different localities is very common. When we consider, moreover, the manner in which furniture and other household material is packed in burlap and excelsior we must realize how common must be the choice of such localities by rats for the making of nests. In the transfer of such articles from place to place, it might well be that the rats themselves were not transported, but their nests, with the fleas in them, would be carried to a new locality, with consequent exposure of local individuals to the bites of very hungry fleas. Stephens (*loc. cit.*) mentions such a possible method of infection with infantile paralysis in a girl who lived far from the ordinary centers of habitation, and in whom the possibility of personal contact seemed to be absolutely excluded. This patient, however, had recently received a package of drapery from an infected district in Melbourne. Stephens makes the specific suggestion in this case that infected fleas might have been transported in this package of drapery. When one considers the geographical relations of New York City in 1916 to the various surrounding communities in Long Island and in New Jersey, not to speak even of Philadelphia or other more distant points, this possible role of flea-infected merchandise seems worthy certainly of attention. Kerley[6] in 1916 followed up several small outbreaks of infantile paralysis which occurred apparently through families which had moved from New York to more or less distant points. In almost all instances the local cases could be explained only by the mediation of "innocent third persons." The possible introduction of infected fleas with the household effects of the newcomers was not, of course, thought of.

Summer Distribution of Infantile Paralysis. This is well shown by Chart 4, taken from a report of the Massachusetts State

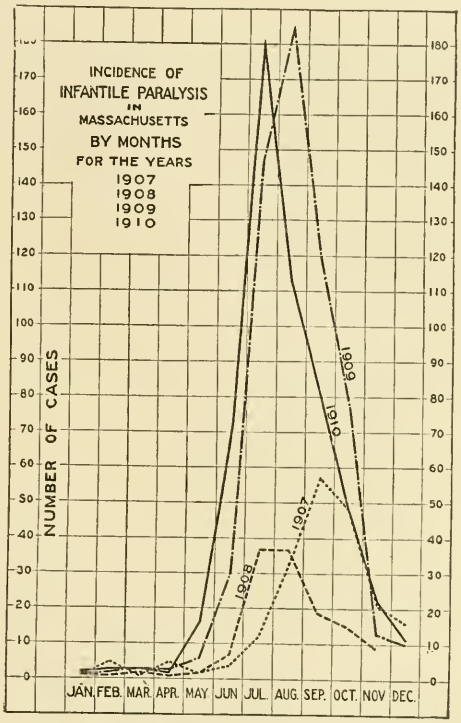
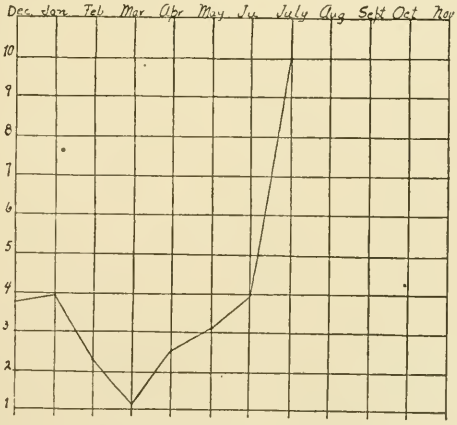


CHART 4.—From Report of Massachusetts State Board of Health, 1910.



Seasonal Abundance of the Cat Flea (*Ctenocephalus felis*).

CHART 5

Board of Health. When we compare this with the seasonal abundance of the cat flea[7] as shown by Chart 5 there certainly appears a striking parallelism. The winter persistence of small numbers of fleas would explain the occasional winter cases of infantile paralysis, and winter epidemics would occur when, through unusual

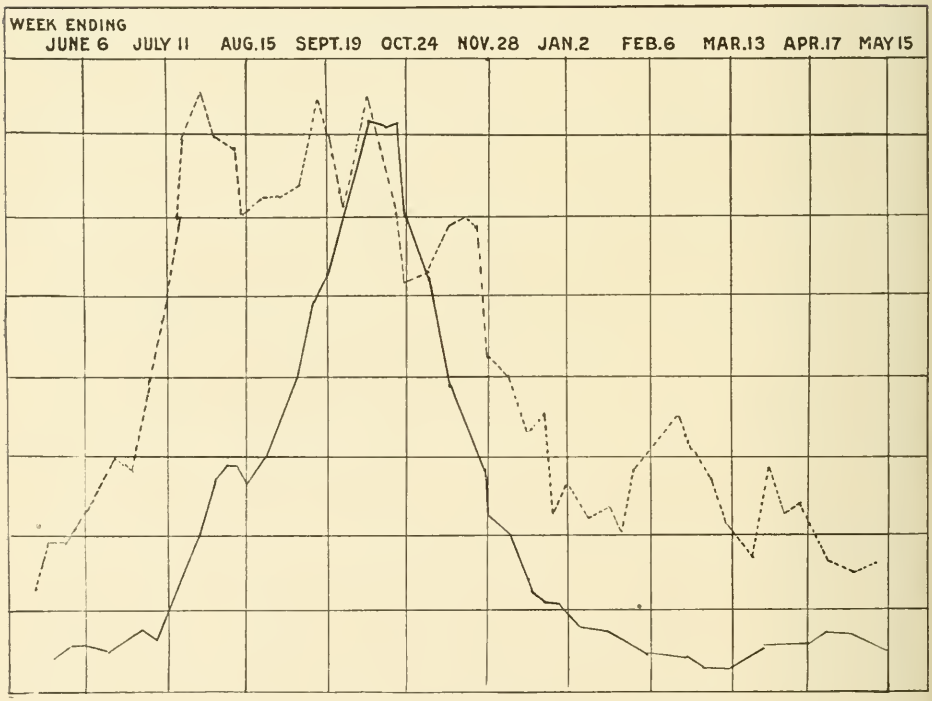


Chart 6.—From Report of British Plague Commission.

conditions, fleas persisted in more considerable numbers. In bubonic plague, the human curves and the flea curves are nearly coincident. (See Chart 6.) It will be noted that human cases do not occur until the flea level has reached a certain height and that the human cases do not persist after the flea level has dropped

beyond a certain point. In San Francisco, Blue found plague in the rats for months after the last human case had occurred.

Interrupted Epidemics. The descending flea curve would explain what may be called *interrupted epidemics*, and which are seen especially in the late fall or early winter. Of the 1914 epidemic in Vermont, Caverly says: "The epidemic began in the village of Barton, the first cases occurring respectively on July ninth, eighteenth, and twenty-second. The *first* cases occurred in that neighborhood in Barton Village, where the *last* cases in the outbreak of 1913 occurred in the month of November." As stated previously, the first cases in Barton in 1914 were located near the grist mills. Why did not the 1913 focus in Barton continue through the winter; or why did it not recur in the earlier months of 1914, for it is quite apparent that the infection persisted in one spot through the winter? If we refer again to Chart 5, showing the cat-flea curve, we find that not until July does this curve reach any abnormal height. The coincidence of this sudden jump in the flea curve with the reappearance of the infantile paralysis cases in July, is certainly striking and suggestive.

Influence of Geological Formation. A study of infantile paralysis in Philadelphia by Dr. Charles S. Miller[3] brought out the interesting fact that geological formation of the land may be of importance. He divided up the city into four principal classifications: sand and gravel, feldspar-mica, rock and quartz, tidal flats, and mixed formation, with the following result:

PHILADELPHIA CASES BY WARDS

Geological formation.	Wards.	Area in acres.	Population per acre.	Cases.	Rate per 100,000 population
Sand and gravel	21	15,212.16	39.294	111	18.56
Arkose sand and gravel	9	8,072.32	42.941	67	13.55
Quartz, feldspar, etc.	2	11,435.8	9.246	35	33.09
Tidal flats	1	5,199.44	8.046	21	50.21
Mixed	10	38,927.36	9.854	86	22.40

Miller says, concerning this table: "It will be noted that the density of population per acre is greater in the sand and gravel groups, and the rate of morbidity per 100,000 population is greater in the section of city overlooking the tidal flats." A greater prevalence of rats over tidal flats is highly probable.

Relation to Water Fronts, Sewers, Slums, Rivers, Brooks, etc. The relation of bubonic plague to these localities is marked. Brues found in New York City (1916) a special grouping of cases on the water fronts. (See Chart 7.) The same was true of Boston in 1916. In Boston in 1916 at least two sailors working on the affected water fronts, acquired infantile paralysis and died.

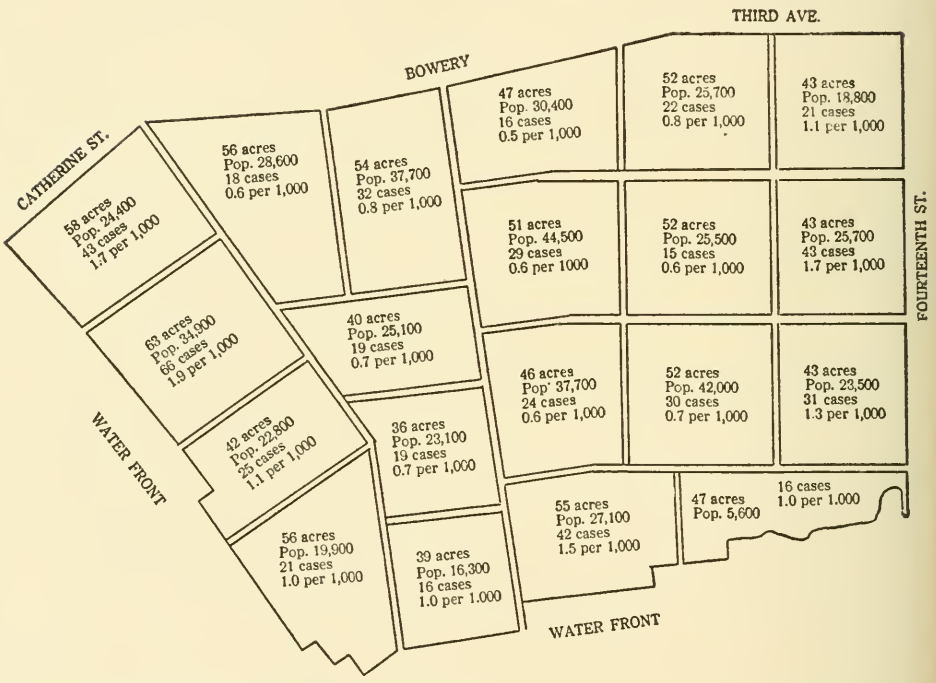

THIRD AVE.
BOWERY
CATHERINE ST.
FOURTEENTH ST.
WATER FRONT
WATER FRONT
58 acres Pop. 24,400 43 cases 1.7 per 1,000
56 acres Pop. 28,600 18 cases 0.6 per 1,000
54 acres Pop. 37,700 32 cases 0.8 per 1,000
47 acres Pop. 30,400 16 cases 0.5 per 1,000
52 acres Pop. 25,700 22 cases 0.8 per 1,000
43 acres Pop. 18,800 21 cases 1.1 per 1,000
51 acres Pop. 44,500 29 cases 0.6 per 1000
52 acres Pop. 25,500 15 cases 0.6 per 1,000
43 acres Pop. 25,700 43 cases 1.7 per 1,000
63 acres Pop. 34,900 66 cases 1.9 per 1,000
40 acres Pop. 25,100 19 cases 0.7 per 1,000
46 acres Pop 37,700 24 cases 0.6 per 1,000
52 acres Pop. 42,000 30 cases 0.7 per 1,000
43 acres Pop. 23,500 31 cases 1.3 per 1,000
42 acres Pop. 22,800 25 cases 1.1 per 1,000
36 acres Pop. 23,100 19 cases 0.7 per 1,000
55 acres Pop. 27,100 42 cases 1.5 per 1,000
47 acres Pop. 5,600
16 cases 1.0 per 1.000
56 acres Pop. 19,900 21 cases 1.0 per 1,000
39 acres Pop. 16,300 16 cases 1.0 per 1.000

Chart 7.—Population 539,300; 545 cases; incidence 1.01 per 1000.—Part of the lower east side of Manhattan, showing the area, population and incidence of poliomyelitis in the several sections. New York City Report, 1916.

Furthermore, although the well-to-do do not escape infection with infantile paralysis, I agree heartily with the statement of Dr. Charles K. Mills of Philadelphia that a very great majority of cases occur in surroundings which are unsanitary and have all the earmarks of rat and flea infestation. As to the cases among the rich, the proximity of stables, the possession of cats and dogs, and the

constant influx of packages of merchandise may well bring about the necessary rat and flea influence essential to infection.

Infantile Paralysis in the Trenches. As is well known, the trenches in the war area are overrun with rats, these rodents having been driven into the open by the destruction of houses, barns, etc. Under the rat theory, infantile paralysis was to be expected among the soldiers, though, of course, adults are not highly susceptible to the disease. Such a small epidemic of ten cases has been described by Etienne.[9] It was confined to a sharply defined section of trenches and to a definite body of troops. The affected troops had no more infantile paralysis after they left the special trenches, and the troops which occupied the trenches after them did not have the disease. The history suggests a contagious agent with a very short period of activity, restricted possibly to an intermediary cycle in an insect. This self-limitation of epidemics to one period of a few weeks has been noted by several observers. Frost, for instance, pointed out the fact that in a city, epidemic infantile paralysis was on the decrease in one ward while rising in a neighborhood ward. (See Chart 8.) This same phenomenon has been noted in bubonic plague in Rohtak, India, by the Indian Plague Commission. In New York City in 1916 "very exceptionally were secondary cases separated from the primary case (in the same family) by a longer interval than two weeks. Similar results were obtained in the study of multiple cases in one house; the majority of the cases would appear to have had a simultaneous infection." (New York City Report for 1916, p. 121.)

Radial Distribution. Bubonic plague is said to spread (*a*) by contiguity and (*b*) *per saltum*. A considerable number of cases will group themselves together in neighboring houses then a leap (*per saltum*) will take place and a new collection of cases will develop by contiguity. Between the two foci will be an area entirely unaffected. This phenomenon in plague is due, of course, to migration of infected rodents, but it is also quite characteristic of infantile paralysis. A remarkable example of radial spread is shown in Chart 9, taken from the 1912 Swedish Report. It is impossible to believe that so regular a distribution could be caused by human beings with their irregular comings and goings. A pre-

liminary gradually spreading rodent infection seems much more reasonable and probable.

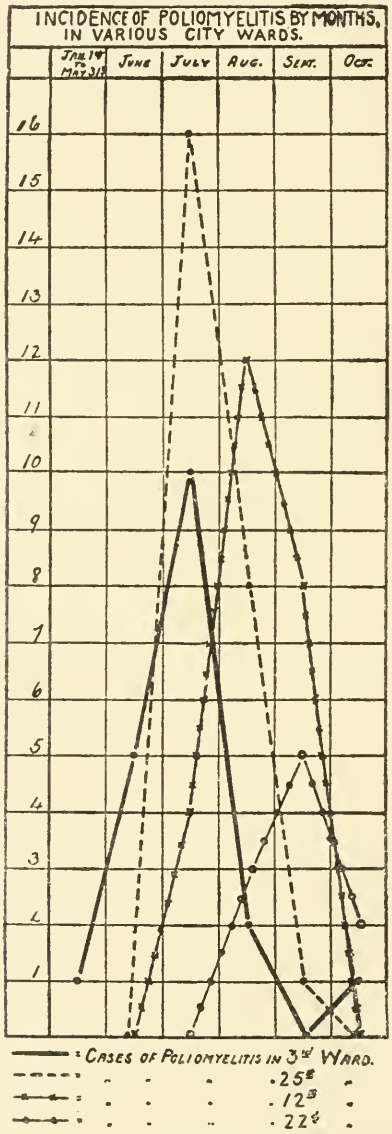


CHART 8.—Buffalo, New York (Frost), 1912.

Seat of Primary Infection. In bubonic plague the primary bubo is, in the great majority of instances, in the groin. This is,

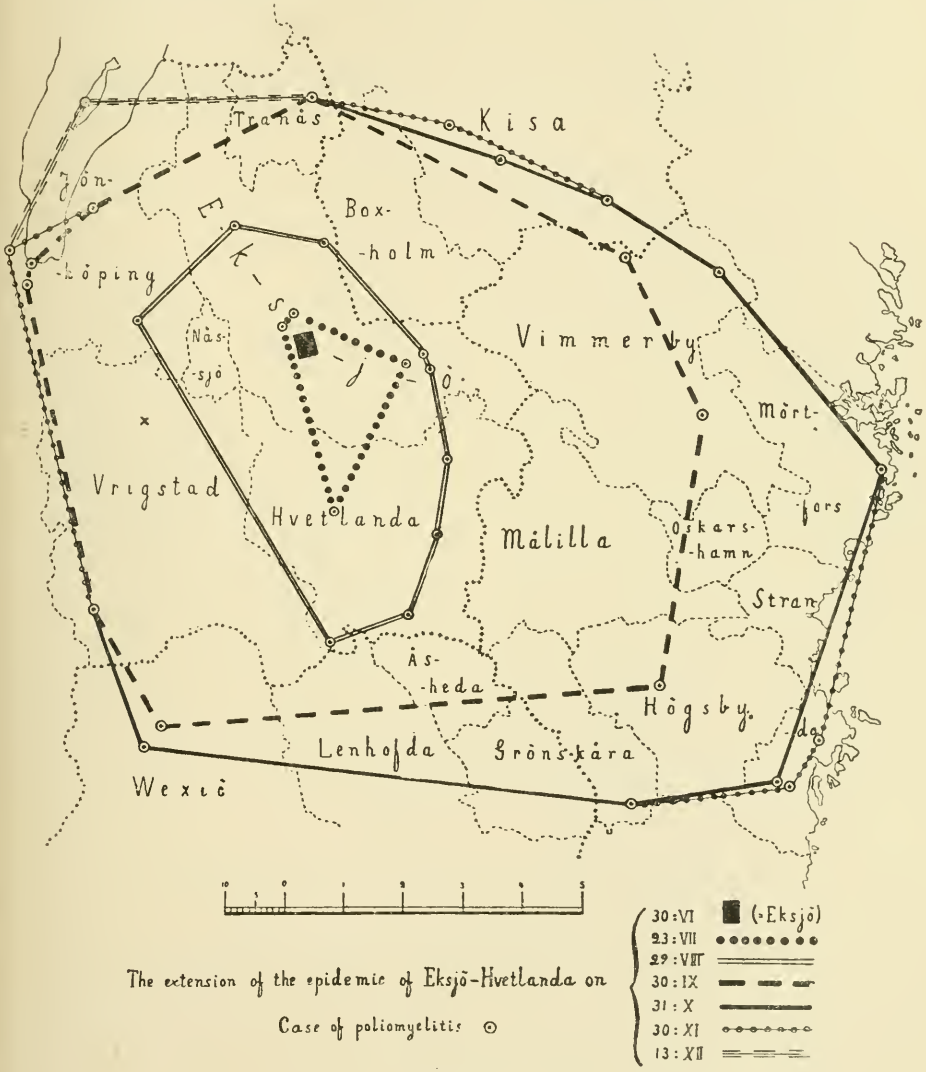


Chart 9

of course, because the flea reaches most easily the legs of his victim. In infantile paralysis, the vast majority of children are paralyzed

in the lower extremities either alone or in combination with other parts of the body. (See Chart 10.) We have, furthermore, the following experimental data as determined by Zappert, Leiner, and Wiesner.[10] These observers found it to be practically always true that in monkeys the initial paralysis depended upon the site of the inoculation. If the inoculation was made into the sciatic, then the

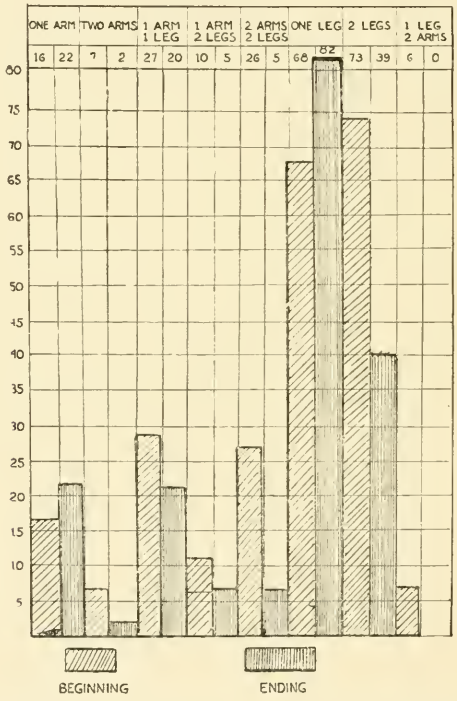


CHART 10.—Showing predominance of lower extremities in initial and final paralysis of human beings. (Zappert, Leiner and Wiesner.)

initial paralysis came in the leg; if into the median, then the arm, etc., the infection travelling along the lymphatics to the spinal cord. The above-mentioned writers suggested that, paralyzed legs in children being in marked predominance, infection might have taken place, in some instances at least, as in tetanus, through breaks in the skin of the lower extremities. The possible relation of flea bites to this aspect of the disease did not occur to these writers

probably because, in 1909, the rat and flea theory of bubonic plague had not been fully substantiated. The conclusion, of course, which I desire to draw from these combined observations is that this marked excess of paralysis in the lower extremities is strong presumptive evidence that the infection takes place through the lower extremities. The fact that the patients almost never give a history of flea bites is of no contradictory value, for in bubonic plague such a history is rarely forthcoming.

Immunity of a Neighborhood Once Infected. In my previous communication I discussed the immunity enjoyed for one or more years by a place once severely infected, and ascribed this immunity, not to a widespread but unrecognized involvement of a large part of the human population, but to an immunizing of the rat population with, possibly, the inheritance of this acquired immunity. This question has come up in connection with bubonic plague, the rats of one city being much more resistant to plague than those of other cities. The explanation, which might apply equally to infantile paralysis, is that during an epizoötic the susceptible rats die, a very resistant race remaining in the ascendant for a long time.

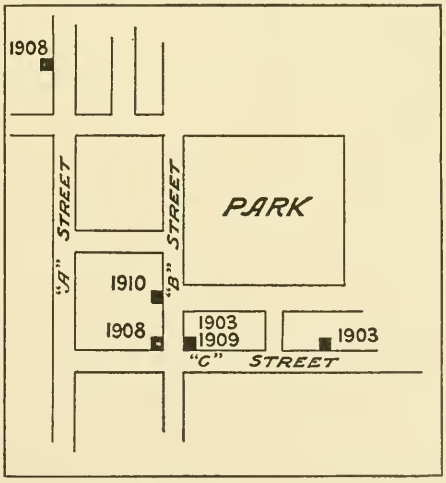


Chart 11.—From Report of Massachusetts State Board of Health, 1910.

Persistence of Infection in Certain Localities Over Long Periods of Time. Bubonic plague is well known to exist in

rats for considerable periods of time before and after the human epidemic. I believe the same to be true of infantile paralysis; that the disease is always present in rats, but appears in human beings only when rat infection and flea infestation are at their

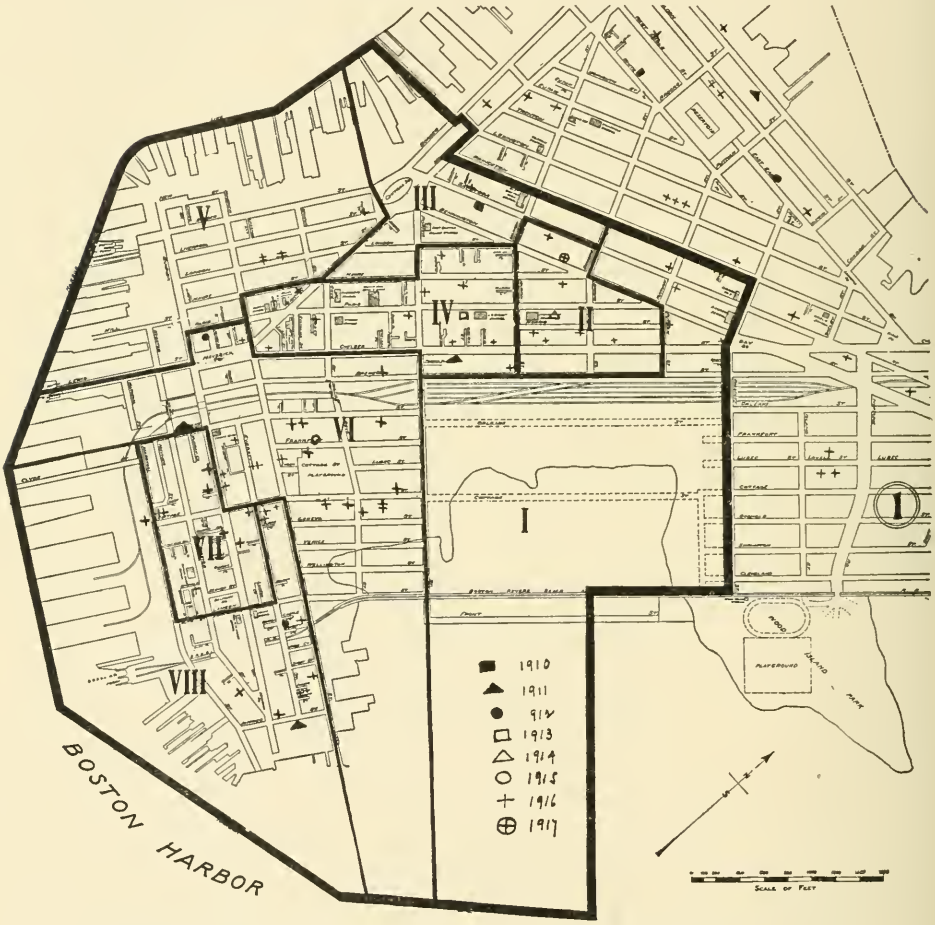


CHART 12.—Showing sporadic cases in off years together with epidemic cases of 1916.

maximum. A third factor is probably essential, furthermore, and that is that the rats infected must, in the main, be young rats. That certain streets or even certain houses may be especially prone to the disease is shown by Chart 11. In the Springfield epidemic

of 1912, three houses which had been infected in 1910 showed instances of infantile paralysis. They were, however, in different families. Wickman mentions a case where a family having suffered from the disease moved out in October. A child of a family which moved in shortly afterward came down with infantile paralysis within a few weeks. A study of Boston cases over a series of years shows very clearly how infantile paralysis persists in sporadic form over considerable periods of time. (Chart 12.) There has been no explanation forthcoming as to why single cases in any year do not spread, especially where, through congestion of the population, abundant opportunity for personal contact is at hand. Such a situation, however, is easily explained by the rat and flea theory because, according to this hypothesis, there can be, just as in bubonic plague, no well-marked human infection until the rat and flea curve have risen to a certain point. Ordinarily this rodent level is low and projects beyond the human level only occasionally. Under extraordinary conditions, however, the level rises rapidly and to such heights that the human involvement reaches epidemic proportions.

Multiple Cases and the Rat Theory. Another point of similarity shown by infantile paralysis and bubonic plague is seen in the fact that it is rare to have more than one case in a single house or family. The Massachusetts figures for infantile paralysis are as follows:

Families with more than one case (1908–1910):*

	Cases.	Per cent.
One case	357	92.24
Two cases	27	6.97
Three cases	3	.77
Total	387	

For bubonic plague in Sidney, Australia, the figures are as follows: 289 cases lived in 216 dwellings; 266 had single case only.

Summary. 1. Although the virus of infantile paralysis has been demonstrated (*a*) in the secretions and excretions of persons sick

* The inclusion of abortive cases in this table would increase the percentage of multiple cases somewhat, but not enough to vitiate the argument. In New York City in 1916, 96 per cent. of the families affected had one case only.

with the disease and (*b*) healthy third persons who have or hav not been in contact with patients, and although such secretions and excretions may in animal experiment remain active for many months, the epidemiological facts are strongly against the theory that infantile paralysis is spread from person to person by direct or indirect contact. On the other hand:

2. The epidemiology of infantile paralysis corresponds so remarkably with that of bubonic plague, a disease known to be due to the rat and flea, that it can be stated with great probability that human infantile paralysis is due to a precedent and underlying infection of rodents.

3. As with bubonic plague, final proof as to the role of the rat and flea in infantile paralysis must rest in elaborate laboratory investigation.

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1. This investigation has been supported by a fund contributed to the Massachusetts General Hospital by the following gentlemen: James J. Storrow, Charles Jackson, Wallace Pierce, Arthur Perry, James H. Proctor, R. L. Studley, Allan Emery, William Endicott, and Frank G. Webster (of Boston). Also J. P. Morgan and Albert Strauss (of New York); Alvah Crocker and George R. Wallace (of Fitchburg, Mass.); and Winthrop Murray Crane (of Dalton, Mass.). Thanks are due furthermore for special privileges to Dr. Francis X. Mahoney, Health Commissioner of Boston, and to Dr. Francis P. Denny of the Brookline Board of Health.

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MYRTOL POISONING

With Comments upon the Toxicity of Eucalyptus Oil and Myrtol in Human Beings and in Animals

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On account of the toxic symptoms that sometimes follow the administration of oil of eucalyptus and allied substances, it would seem worth while to report the following case of alleged poisoning by myrtol:

Clinical History. The patient, a gentleman, aged forty-two years, consulted one of us on January 10, 1911, complaining of cough with a large amount of offensive sputum. The family history is negative for tuberculosis. The patient had pneumonia at the age of twenty-one, since when he has had more or less cough and sputum. During the past five years the cough has been worse and a considerable amount of sputum has been coughed up each morning. Five years ago, after an acute cold with sore-throat, he suffered from hemoptysis, coughing up half a teacupful of blood. Repeated examinations for tubercle bacilli were made, but none were found. There was no fever during the attack. In September, 1911, before consulting us, he had had an acute bronchitis accompanied by slight hemoptysis. This was followed by a bronchopneumonia involving the upper lobe of the right lung, the illness lasting over one month. Many examinations for tubercle bacilli were made during this period, always with negative results. An autogenous vaccine was

prepared by his local physician against some microörganism grown from the sputum and five doses were administered.

Note made on January 10, 1911 (Dr. Barker). The patient now feels very well, though he still coughs up a considerable amount of sputum, especially in the morning, and this sputum is very offensive at times. The total amount raised now is about four ounces in the 24 hours. There is no pain and no dyspnea. The voice is occasionally hoarse. No night-sweats. No marked digestive disturbance. Weight, 227 pounds. Height, 6 feet 2 inches. The weight was 245 pounds before the attack of broncho-pneumonia.

Physical Examination. Slight protrusio bulborum; positive von Graefe's sign. Defective teeth. No struma. No glandular enlargements. Right upper chest flatter than left in front. Right mammilla on lower level than left. Expansion greater in left chest; right lung lags behind. Breath-sounds slightly prolonged at right apex, and the percussion note is a little higher pitched there than on the left. No rales audible in upper lobes. Fremitus somewhat more marked over the right suprascapular region than over the left. Breath-sounds distant at the right base. A distinct creaking sound is audible at the right base, and some distant moist rales can be heard there. Breath-sounds and voice-sounds are distant over right lower lobe behind. Heart negative. Abdomen negative. Reflexes normal.

X-ray Examination (Dr. F. H. Baetjer). Stereoscopic and radiographic examination of the chest shows increase of fibrous tissue around the bronchi and the bronchial ramifications in both lungs. Some enlarged glands at the hilum of the left lung. Left lung substance clear throughout. A peculiar shadow is seen at the base of the right lung, obliterating the diaphragm and the base of the right lower lobe. This shadow is probably due to thickened pleura and to some fibroid change in the lung itself. In the upper part of the right lower lobe the bronchial tree can be distinctly made out. There is a suggestion of a bronchiectatic cavity in the right lower lobe, but there is so much fibrous peribronchial change that no definite statement regarding it dare be made.

Diagnosis. Bronchiectasis; bronchitis chronica putrida; peribronchitis fibrosa; pleuritis chronica dextra.

Treatment. In addition to general measures, three minims of myrtol in capsules thrice daily were prescribed on account of the fetid bronchitis. The patient had been taking some oil of eucalyptus and oil of sandalwood before. These he continued along with the myrtol.

Further Course. January 16. The patient reports that the myrtol is already lessening the putrid odor of the sputum.

February 13. The patient writes from the Pacific Coast that he has suffered strange and severe symptoms since taking the myrtol prescribed. After having taken two capsules three times a day for eight days, "the face became discolored and large 'puffs' came under each eye. The forehead looked as if it were going to break out with eczema. The left eye became nearly closed and the right partially closed from the swelling." Fearing an attack of erysipelas he called a local physician, who, with the nurse, agreed that the symptoms must be due to the poisonous effects of the myrtol. The drug was stopped at once, but the swelling lasted for many days. The patient states that the cough increased markedly and that the heart's action became more rapid, and that he was greatly depressed. He had been told to increase the dose of myrtol gradually until twelve capsules per day were taken, but the myrtol was stopped when only six capsules per day were ingested. He states that the discoloration of the skin and eruption covered the entire chest also.

February 28. The patient writes that he and the nurse feel entirely convinced that the whole trouble was caused by the myrtol. He sends the bottle containing the unused portion of the drug that experiments may be undertaken with it. It was purchased from a druggist in Baltimore, who stated that it had come direct from Merck's, in New York. In one of the patient's later letters he states that he is not sure that the offensive odor of the breath was really decreased by the myrtol. He also states that while on the train going toward the Pacific Coast, during the last two days of the trip, he was in serious doubt as to whether he would reach his destination alive. Here we have evidently to deal with an instance of myrtol intoxication, probably exaggerated by the oil of eucalyptus which was taken at the same time. The striking phenomena observed in this patient, never before observed by us notwithstanding a considerable earlier experience in myrtol administration, led us to try some experiments on animals and to review the literature of the subject.

Sources of Myrtol and Eucalyptol. Myrtol, obtained by distillation from the leaves of *Myrtus communis*, is a mixture of a dextrorotary terpene (known as cineol), pinene, $C_{16}H_{18}O$ and dipentene. The myrtol, on distillation, comes over between 160° and 180° C.

Oil of eucalyptus is a volatile oil distilled from the fresh leaves of eucalyptus, rectified by steam distillation; it yields, when assayed, 50 per cent of eucalyptol.

Eucalyptol ($C_{10}H_{18}O$) is the chief constituent of the eucalyptus

oil obtained from *Eucalyptus globulus* and some other species. It is an organic oxide (optically inactive) isomeric with cajeputol (levorotary) and with cineol (dextrorotary). In the distillation of eucalpytus leaves the portion that comes over between 170° and 178° C. is set aside as crude eucalyptol. When redistilled from potassium hydroxide, pure eucalyptol is obtained.

The large natural order, *Myrtaceæ*, includes many genera. Among them besides *Eucalyptus* and *Myrtus* may be mentioned *Pimenta* (allspice) and *Eugenia* (cloves). The oils from these several myrtaceous species are utilized to a considerable extent as remedial agents.

Eucalyptus oil, eucalyptol and myrtol find their chief value in therapeutics, at present, in the treatment of catarrhal conditions of the respiratory mucous membrane; they are administered either internally (on sugar, or in capsule) or with steam in the vapor from an inhaling apparatus. They are also occasionally employed (1) in chronic inflammation of the genito-urinary mucous membranes; (2) locally as an antiseptic dressing to ulcers; and (3) also as counterirritants in neuralgia and rheumatism. Eucalyptus oil and eucalyptol are usually administered in 5 to 10 minim doses and myrtol in 5 to 15 minim doses, in capsule, four to eight times a day.

Formerly, eucalyptus oil was utilized much more extensively than at present. It was thought to possess considerable value as an antiperiodic and hence was widely used in the treatment of malaria. It was administered in these cases in large doses (usually from ½ to 1 dram) two or three hours before the expected paroxysm. The subcutaneous administration was frequently resorted to, the oil being diluted in olive oil (1 in 4 or 1 in 10). It has also been used locally in the treatment of varous skin diseases, *e. g.*, in eczema, prurigo, psoriasis, impetigo and condylomata. Recently, since Dakin's introduction of chloramin therapy, oil of eucaylptus has begun to be extensively used and it will be interesting to observe whether many instances of intoxication are met with.

Animal Experiments (Dr. Rowntree). Some experiments were made upon dogs and cats with myrtol and with eucalyptus oil in order to determine their toxicity. The data relating to the

myrtol experiments are first presented. Since the bottle of myrtol used by the patient was only partially emptied, the remainder was available for study. It is here designated as Preparation I. Another sample of myrtol (Preparation II) was obtained from a local druggist. The drug was administered to the animals through a stomach-tube.

EFFECT OF MYRTOL ON DOGS

Dog.	Weight in kg.	Date.	Amount administered.	Condition of animal.
I	9.9	3-11-11	1 c.c. of Prep. I.	No abnormality noted.
		3-13-11	5 c.c. of Prep. I.	Dog did not vomit this. He took his food and drink normally. He remained normal.
II	9.3	3-11-11	0.8 c.c. of Prep. I.	This dog remained perfectly normal throughout the period of observation from March 11 to March 25.
		3-12-11	2 c.c. of Prep. I.	
		3-14-11	2 c.c. of Prep. I.	
		3-15-11	2 c.c. of Prep. II.	
III	6.2	3-13-11	2 c.c. of Prep. I.	Vomited five minutes after first administration. Remained free from vomiting after other doses until the 22d. On this date the dog vomited 10 minutes after the administration. The vomited oil was intimately mixed with meat. The dog ate this again and was entirely normal after it. No sign of a skin lesion developed.
		3-14-11	0.5 c.c. of Prep. I.	
		3-15-11	2 c.c. of Prep. II.	
		3-16-11	2 c.c. of Prep. II.	
		3-17-11	2 c.c. of Prep. II.	
		3-18-11	2 c.c. of Prep. II.	
		3-19-11	2 c.c. of Prep. II.	
		3-20-11	2 c.c. of Prep. II.	
		3-21-11	2 c.c. of Prep. II.	
		3-22-11	2 c.c. of Prep. II.	
IV	5	3-15-11	0.5 c.c. of Prep. I.	This dog remained absolutely normal until the 21st. On this date coryza and diarrhea were noted. Dog developed a typical distemper and so was discarded. No skin rash.
		3-16-11	0.5 c.c. of Prep. I.	
		3-17-11	0.5 c.c. of Prep. I.	
		3-18-11	0.5 c.c. of Prep. I.	
		3-20-11	0.5 c.c. of Prep. I.	
		3-21-11	0.5 c.c. of Prep. I.	
V	5	4- 5-11	5 c.c. of Prep. I.	Dog did not vomit. No ill effect noted.
VI	4	4- 2-11	2 c.c. of Prep. II. every day for a period of two weeks.	Outside of a slight loss of appetite no abnormal condition was noted. No rash appeared.

Careful examination of skin was repeatedly made on all of these animals, but at no time was there noted any skin rash ascribable to the drug.

In the following experiments, however, severe toxic phenomena followed subcutaneous and intraperitoneal administration:

Exp. VII. Dog. 7.3 kg. Very playful. Pulse 150, respirations 36, temperature 38°.

12.24 10 c.c. eucalyptus oil in 30 c.c. olive oil subcutaneously.

12.30 Has lost playfulness, will not eat meat. Marked odor to breath. Sits in the corner, saliva dripping from mouth. Pulse and respiration unchanged at 12.40. Dizzy, does not respond well to prodding, apparently somewhat anesthetic.

1.20 Pulse 180, respiration 36; very dizzy.

3.20 Staggering, lies in a corner. Feces and urine passed and the dog lies in them. Pulse 180. Pupils normal.

5 P.M. Respiration 30, temperature 39°. Marked collapse. Pulse cannot be felt, but a rate of 200 is determined by auscultating heart. Dog has been lying in her urine and feces; can scarcely walk. Pupils slightly larger than normal, and contract to light.

7 P.M. Condition unchanged.

The following morning the animal had the odor of eucalyptus on its breath, but was running about, apparently in normal condition. Pulse 104, respiration 24, temperature 37.5° C.

Two days later: odor still present in breath. Feces and urine free from odor. Dog normal.

Exp. VIII. A cat (1.8 kg.) was given subcutaneously 5 c.c. of Preparation II in 15 c.c. olive oil on December 8. After ten minutes it seemed somewhat restless, but otherwise normal. The pulse, respirations and temperature remained unchanged during a period of observation of five hours. On December 9 the animal was somewhat ataxic, presenting a staggering gait. It refused to eat or drink. The breath smelled strongly of eucalyptus oil. The pupils remained normal. The urine was dark in color, showed a trace of albumin, but no sugar. Casts and blood were absent. Respiration, pulse and temperature normal. On the following day the animal was much better, walked without staggering, but still refused water and food. Urine showed a slight trace of albumin. On December 11 it drank milk and took its food and was apparently normal again.

Exp. IX. Eucalyptus oil in toxic doses was also administered to two cats. Cat I (2 kg.) was given 10 c.c. of eucalyptus oil in 30 c.c. of olive oil intraperitoneally at 12.30. At 12.38 it appeared unsteady on its feet and swayed from side to side when attempting to walk. Stringy mucus was secreted from the mouth. At 12.40 it huddled up in a corner and refused to move. At 12.47 all power of motion was lost. The animal apparently was anesthetized, inasmuch as no response to prodding with a needle could be elicited. A slight clonic convulsion was seen at 12.50. This became more marked, following any sudden sharp noise, *e. g.*, clapping of hands. Respiration normal, pulse 112. Temperature 37° (normal, taken before giving oil, 38.5° C.). The pupils remained normal. Animal comatose. Death at 2.30 P.M.

Exp. X. Cat II (1.8 kg.), 10 c.c. eucalyptus oil at 1 P.M., subcutaneously. The animal appeared dizzy at 3 P.M., staggering on attempting to walk. At 8 P.M. this was more marked. The following morning the animal was found in a semi-comatose condition. Convulsions occurred at intervals. Temperature was low, 29° C., by rectum. Pulse 92, respirations 14. Urine high colored and scanty, containing blood and albumin, but no casts. The odor of eucalyptus on breath was very marked. Chlorobutanol gm. 1.0 was administered, followed by death in the course of an hour.

Bruning has determined the toxicity of eucalyptus oil for animals and finds that, in the frog, 0.5 gm. per kilo caused only temporary paralysis, in toads 1 gm. per kilo did not kill constantly, in fish a solution of 1 to 10,000 was tolerated, in chickens 0.3 c.c., in rabbits 1 to 5 c.c., and in guinea-pigs 1 c.c. per kilo was not fatal. He states that small doses are dangerous to children and advises against its employment in the treatment of ascaris lumbricoides.

REVIEW OF LITERATURE. In looking over the literature nothing seems to be recorded regarding the toxicity of myrtol, but with eucalyptus oil we find that cases of poisoning have not been uncommon. The cases reported may be divided into two classes:

I. Cases in which overdoses have been taken accidentally or through ignorance, following which grave symptoms of intoxication have been present; some of the patients recovered more or less gradually, though some died.

II. Cases in which the patient has responded in an unexpected and unaccountable way to minute or therapeutic amounts of eucalyptus preparations.

CASE I.—Beginning with cases of the first class: Wood (1879) reported a case of poisoning with belladonna and eucalyptus. A man, aged 48, received ½ ounce of belladonna root together with 3 drams of eucalyptus oil. Six hours later, when first seen, he was unconscious, with widely dilated pupils which did not respond to light. Pulse 110, full and strong; respirations rapid. Spasmodic twitchings of the extremities. After the stomach had been emptied with a tube, the patient was stimulated electrically and on partial revival was made to move about and to walk between assistants for a period of five hours. At the end of this time he was still in a dazed condition and hyperesthetic over the whole skin. Strong coffee and milk were given and also 4 minims of tincture of opium. On the following day, dryness of the throat, thirst and pruritus were complained of. At the same time, the skin of the patient showed a red blush, which

lasted for two days. At the end of two weeks, the patient left the hospital, apparently in a normal condition.

Case II.—Owen (1885) made a report of a child, 17 months old, who swallowed the drippings from a bottle of fluid extract of eucalyptus. Within a half hour it became drowsy and lost all power in the limbs. The child was pale, its head and extremities were cold, the pupils were contracted, the conjunctivæ were insensitive, the pulse was imperceptible, and the respirations were short and spasmodic. The child could be aroused. Following a soap and lime water emetic, it vomited three times. Whisky, warm milk and lime water were administered; the child was put to bed and artificial heat applied. Two and a half hours later, the pulse was feeble and small, but the patient was less drowsy. Castor oil was then administered. The temperature rose, and thirty-six hours after the ingestion of the eucalyptus had reached 102° F.; the respirations were 60 to the minute. A slight cough and rhonchi were noted. Five days later the child had fully recovered.

Case III.—Sheaf (1888) reported that a man twenty-five years old developed vertigo one and one-quarter hours after taking 5 drams of eucalyptus oil. The patient talked loudly, and exhibited involuntary twitchings of the fingers. He did not vomit. He was conscious two hours later, but the pulse was weak and rapid. Emetics were used and caffein and sodium salicylate administered. The patient recovered completely.

Case IV.—Wood (1888) cited a case of Gimbert's: An old man took 80 minims of eucalyptus oil. The power of motion almost disappeared and the patient affirmed that he had lost, for the time being, all sense of the presence of his limbs, so that he was unconscious of them when he shut his eyes. His intellect was perfectly clear throughout.

Case V.—Wood also stated that Binz had described a similar condition after 75 minims had been taken.

Case VI.—Neal (1893) reported that a healthy boy, ten years old, took some eucalyptus (½ dram of blue gum) for prophylactic reasons just before going to bed. In a few moments he was gasping for breath. He vomited and felt much better. Dyspnea became marked, however, one hour later, but no convulsions or diarrhea were noted. The lips and gums were colorless, the chest and neck rigid, and the pulse feeble and rapid. He complained of pain in the right chest, which was relieved by poultices. The intellect remained clear until one hour before death. At the autopsy, the stomach was found to be much distended with gas, the gastric mucosa being white, thickened, and puckered. There was a quart of fluid in the pleural cavities; the lungs were collapsed, firm and bloodless. The right heart contained frothy liquid blood.

Cases VII and VIII.—Neal quoted Martindale as having given 80 minims of eucalyptus oil in two and one-half hours. He also mentioned

a case in which Croker of Geeling had asserted that a man's death was accelerated by a dose of 1 ounce of eucalyptus.

Case IX.—Lewin (1897) stated that a boy, sixteen years old, after taking 15 grams of the oil vomited and went into a state of collapse. Dyspnea and air hunger were noted. The boy died within fifteen hours, and at autopsy blood was found in the pleural cavities.

Case X.—Manquat (1898) speaks of Siegen's case in which the ingestion of 3.5 grams of the oil of eucalyptus was followed by headache, drunkenness, stupor, somnolence, weakened reflexes, enfeebled respiration, lowered blood-pressure, decreased temperature, and eventually by paralysis of respiration.

Cases XI and XII.—Kunkel (1899) describes two cases: (1) A child, three years old, took a small spoonful of eucalyptus oil. He estimated that the amount was about 8 grams. Vomiting was followed by speedy recovery. (2) A boy, ten years old, took 15 grams of eucalyptus oil and died in collapse fifteen hours later.

Case XIII.—Thomas (1899) reports the poisoning of a baby boy, four weeks old, with 1 dram of eucalyptus oil. When seen the patient was comatose; harsh breathing and the odor of the drug on breath were noted. Ipecac was given and repeated in one-half hour. Stimulants were of no avail. Death occurred four hours after the administration of the oil. There was no emesis.

Case XIV.—Wood (1900) reported that a child three years old grew violently sick within two hours after taking 2 or 3 drams of the oil. Drowsiness, stupor and collapse developed, along with pin-point pupils. The symptoms lasted ten hours, but the patient recovered. Except for the absence of stertorous breathing, the condition was described as identical with that encountered in opium poisoning.

Case XV.—Taylor (1905) stated that a man, twenty-five years old, took 1 dram of eucalyptus, and within a few minutes had pain along the esophagus and in the gastric region. After a time he became dazed and suffered from a feeling of impending suffocation. He was at first very restless, but later became semi-comatose. The pupils were slightly contracted. Emetics and stimulants were successfully employed, and the following morning the patient was apparently well.

Cases XVI and XVII.—Benham (1905) reported two cases: (1) A man, forty-one years of age, became comatose after swallowing 1 dram of the oil. Emetics were successful; the man was entirely well in a few hours. (2) A young man showed similar symptoms after 1 dram of the oil. Emetics were employed and the patient recovered.

Case XVIII.—Smith (1906) investigated a case of poisoning by half a wine-glass full of eucalyptus oil. The particulars concerning the patient are not given, but the oil was a "cineol eucalyptus oil" and a good preparation of the kind.

Case XIX.—Orr (1906) stated that a boy, two years and nine months old, took 2 drams of the oil and was seen fifteen minutes later. He was in collapse, unconscious, had a very rapid pulse, and his breathing was stertorous. The pupils were contracted to a pin-point. He vomited early and was purged. Zinc sulphate was given and was followed by emesis. Whisky and coffee were then given. One hour later consciousness had returned and the patient was well.

Case XX.—Benjamin (1906) records the case of a boy, eight years of age, suffering from intermittent fever, who was given 6 drams of eucalyptus oil at 5 A.M. He vomited half an hour later. At 7 A.M. he became unconscious; vomiting recurred several times before 11 A.M. At this time he was found in partial collapse, the pupils were contracted and the breathing labored. The temperature was 99.8° and the pulse 128. The abdomen was tympanitic. Hiccough was troublesome. The treatment consisted of cold applications to the head, mustard on the neck, an ammonia mixture internally, and enemata. At 3 P.M. the patient regained consciousness. No after-effects were noted.

Case XXI.—Myott (1906) observed a man, thirty-four years old, a heavy drinker, who took 6 drams of eucalyptus oil. He walked about for two hours, then became dazed and suddenly fell unconscious. Warm water was introduced into the stomach and the patient vomited. Four hours after ingestion of the oil he was cyanotic and the breathing was labored. Frequent attempts to empty the bronchial tubes of a thin, frothy secretion were made. Pulse 128, respiration 24, temperature 97°. Pupils slightly contracted. The patient was then given strychnin and oxygen. The expectoration became thick and blood-tinged, the fever rose continuously, and forty hours after ingestion, just prior to death, the temperature was 103°, pulse 140, respirations 48. The autopsy showed bulky, heavy lungs, some gastritis and some pleuritis.

Case XXII.—Schroeder (1908) stated that a child one and one-half years old exhibited evidence of delirium, coma, vomiting and collapse after an unknown dose of eucalyptus. Recovery was complete in a few hours.

Case XXIII.—Robertson (1909) reported that a man, fifty-five years old, took 5 drams of eucalyptus oil before retiring. He wakened during the night feeling sick, but did not vomit until several hours later. He was terribly prostrated, pale gray in color, and cold to the touch. The pulse, however, remained normal in rate and rhythm. The following afternoon he felt fairly well, and he returned to work within a few days.

Cases XXIV and XXV.—Kirkness (1910) reports two cases: (1) Man, twenty-eight years of age, took between 2 and 3 drams of eucalyptus oil. Ten minutes later, he suffered from dizziness and from marked dyspnea. The pupils were dilated and the pulse was weak and thready. The temperature sank to between 95° and 96° F. The patient vomited and com-

plained of a sensation of girdle-like constriction. The skin was greenish-yellow. He complained of drowsiness, of great coldness, and of intense frontal and occipital headache. Half an hour after ingestion, marked diarrhea set in and also frequent and painful micturition. The feces were dark in color and smelled of the oil. He was given emetics and stimulants, was put to bed and was surrounded with artificial heat. This treatment was followed in a few hours by a return of normal temperature and pulse. For three days, however, he looked chlorotic and showed an ataxic gait. The feces, urine and breath all smelled of the oil for a fortnight after the poisoning. Recovery was complete. (2) A girl of eighteen years took 1 ounce of the oil. She complained of intense headache and vomited. She showed collapse, bodily and mentally. The pulse became very feeble, the temperature subnormal and the pupils dilated. She also complained of a girdle-like constriction. She recovered.

Case XXVI.—Allan (1910) recorded a case of a child, twenty months old; eucalyptus oil was applied to its chest and 1 ounce of the oil was given by mouth. Within twenty minutes the child became very sick and seemed to suffer violent pain. A few minutes later it became semi-comatose and vomited. The pulse was feeble and intermittent, the temperature subnormal; the patient collapsed. Stimulants and artificial heat were employed and two days later the child was reported as well.

Case XXVII.—Jolly (1910) describes a patient, admitted to the hospital for anemia and dyspepsia, who was found to be suffering from ankylostomiasis. Magnesium sulphate was given at night, followed next morning by eucalyptus oil min. xxx, chloroform 45 min. and castor oil 10 ounces in two doses. Two hours later the patient was weak and giddy, and an hour later in collapse. Languor, giddiness, dyspnea, general pains (most severe in the head, abdomen and urethra) were complained of. The respiration became shallow and labored, the pulse weak and irregular, the blood-pressure low, and the pupils dilated. The breath and skin smelled of eucalyptus. Vomiting did not occur; no urine or feces passed. Following the application of a mustard plaster over the heart and the administration of strychnin, atropin, artificial heat and enemata, recovery occurred.

Case XXVIII.—Foggie (1911) reported the case of a boy, six years of age, who took 1 dram of the oil. Four hours later nausea and vomiting occurred, the patient passing into a serious condition of coma and collapse. The case was treated as though it were one of opium poisoning and the recovery was complete.

Case XXIX.—In 1914, Winterbotham reported a case of poisoning by oil of eucalyptus. The patient, a man thirty years old, took a teaspoonful of "the best eucalyptus extract" at 7 A.M. and another at 10 P.M. He noticed no effect until after luncheon, when (at 1.15 P.M.) he became

very pale, began to sweat profusely, and became unable to walk without assistance. He felt drowsy, and retched a little. There was no vomiting and no headache. Winterbotham saw him at 3.30 P.M., and could detect the odor of eucalyptus on his breath. The gait was unsteady. Now and then his talk was nonsensical. The articulation was impaired. The pulse, though weak, was not accelerated. Alcoholic intoxication was ruled out. At 4 P.M., the patient went to sleep and slept heavily until the next morning, when he awoke feeling perfectly well.

Thus, in the above 29 cases, found in the literature, seven ended fatally; all of the other patients appear to have recovered completely within a few days.

Only 5 cases of the second class of cases could be found; that is, of instances in which the patient responded in an unexpected and unaccountable manner to minute or therapeutic doses. These cases are particularly interesting in relation to the one we report.

CASES XXX AND XXXI.—Galewsky (1905) reported two cases in which a skin disease developed as the result of the patient coming in contact with branches of the eucalyptus tree. He asserted that dermatitis not infrequently results after rubbing eucalyptus oil into the skin and he cited one instance in which an acute papular dermatitis followed its use. Galewsky states that he was consulted by a woman suffering from erythematous urticaria. She presented large and small urticarial lesions and the intervening areas showed erythematous spots. The itching was intense and the disease was of long duration. The exposed cutaneous surfaces were particularly involved, but the neck and breast also, though to a less degree. She asserted that this rash would entirely disappear when she was away from home for a considerable length of time, but always reappeared on her return. She stated also that the itching was always more severe when she remained for any length of time in one particular room. Galewsky visited her home and in the above-mentioned room he found branches of the eucalyptus used as an ornament. Thinking that this might possibly be the etiological factor, he ordered it removed. The housemaid scoffed at this idea and to prove the harmlessness of the eucalyptus, moistened some of these leaves and rubbed them on her own skin. At the end of half an hour she exhibited lesions identical with those complained of by her mistress. The eucalyptus was removed and subsequently both patients fully recovered, the rash never reappearing.

CASE XXXII.—Davies (1906) stated that his son fainted on inhaling the vapor of eucalyptus and that on another occasion he had to leave a chapel during service on account of a threatened fainting spell brought

on by the odor of eucalyptus, the leaves being used in the way of decoration. This peculiarity is stated to be inherited from his mother, who also faints on smelling eucalyptus.

Case XXXIII.—Hans Vörner (1907) reported an experience with eucalyptus which proves conclusively that in certain persons it can produce skin lesions. In August, 1906, a patient entered the skin clinic and stated that for two days he had been taking 20 drops of eucalyptus oil and that, after doing so, he had developed a skin rash which itched and burned. He ascribed this to the eucalyptus. On examination, it was found that wheals were present over the entire cutaneous surface. They were chiefly discrete, but in places were confluent. The single lesions varied from 2 mm. to 2 cm. in diameter, while the confluent lesions were in some areas as large as one's hand. They were of a livid red color, the center sometimes slightly blue, and the edges a more intense red. The oil was stopped and the rash promptly disappeared. In order to test the assertion of the patient, the oil was administered again ten days later, whereupon an identical rash appeared within twenty-four hours. Six weeks later the rash reappeared without any oil having been administered. The patient complained, however, of a cold in the head, of headache, and of an intense taste of eucalyptus oil. Identical attacks recurred in November and again in December. For two or three months he remained free, but similar attacks occurred again in March and again in April, but the taste of oil was not present in these last two attacks. During the various attacks the back of the head, the back, abdomen, right breast, arm, thigh and legs were all involved, the hands and feet escaping altogether except for a lesion on one thumb during one of the attacks.

Case XXXIV.—Oppenheim (1912) reported that a tailor, thirty-six years of age, complained of skin lesions developing as the result of taking cough lozenges ("*Huste nicht*"). The backs of the hands, palms, fingers, wrists, and dorsa of the feet showed an eruption, consisting of pea-sized, bright red, cherry-red and brownish-red papules and nodules. These were mostly circumscribed, but were confluent on the fingers and toes, and on the palms and soles of the feet. The color did not disappear on pressure with glass slide. Hemorrhages appeared here and there. There was no desquamation. The mucous membranes were not involved. Slight itching was associated with the eruption. The color changed later to brown. The rash was preceded by anorexia, insomnia, malaise and fatigue, those symptoms appearing two hours after the last tablet was taken.

Discussion. From the preceding analysis, at least two different syndromes emerge as evidences of intoxication with derivatives of myrtaceous plants (eucalyptus oil, myrtol, cineol, etc.), and

we shall venture to designate them respectively as (1) a myrtogenic neuropathy and (2) a myrtogenic dermatopathy, though without prejudice as to whether the terpenes in the oils are the toxic agents or some chemical substance that accompanies them. The dermatopathy may in some of the cases be a special instance of the neuropathy, through the mediation of the autonomic nerves innervating the bloodvessels of the skin, though a true dermatitis seems certainly to have been present in other cases.

The Myrtogenic Neuropathy. In the cases discovered in the literature, the first 29 grouped as Class I (*vide supra*) appear to belong to this category. In a few minutes, or a few hours, after the ingestion of a considerable quantity of the myrtaceous derivatives mentioned, the patients became seriously ill. They were pale, dyspneic and restless, and complained of headache, dizziness, twitching, and of pains (in the chest or limbs). At first, the intellect was sometimes clear, but in many instances the patients soon became drowsy and complained of feeling dazed and of a loss of knowledge of the whereabouts of their extremities. On attempting to walk, they staggered about and sometimes fell. Some patients stated that they felt a girdle-sensation (constriction). In the severer intoxications, they were delirious or suffered from convulsive seizures, and some became comatose, with pronounced symptoms of collapse (tachycardia, arterial hypotension, pallor and slight cyanosis, cold extremities, diminished reflexes, hypothermia). Vomiting and diarrhea were common accompaniments of the intoxication. It is fortunate when these symptoms occur, and if vomiting does not occur spontaneously, it should be induced, or the stomach should be washed out to prevent further absorption of the poisonous substance.

The behavior of the pupils has been variable; in most cases, there was extreme myosis; in some instances, outspoken mydriasis was observed. It seems likely that the myosis indicates an irritation of the midbrain autonomic system, the mydriasis a paralysis of the same. In the domain of the pelvic division of the craniosacral autonomic system, the patients sometimes complained of pollakiuria and of dysuria.

The pleural effusion reported in two of the cases deserves especial

mention; in Neal's case, a quart of fluid was found in the pleural cavities; in Lewin's case, a bloody effusion was observed. Whether these pleural phenomena were accidental accompaniments or were actually due to the intoxication must be left to later studies to decide.

Several observers have been struck with the resemblance to poisoning by opium, but they emphasize the absence of the stertorous breathing that accompanies that intoxication.

The Myrtogenic Dermatopathy. In four cases in the literature, and in the case we report ourselves, remarkable cutaneous manifestations followed the ingestion of myrtaceous derivatives. In our own case, the skin lesions were associated with marked nervous symptoms (great depression; symptoms of collapse).

The lesions in the skin vary in their nature: Sometimes merely (1) *erythematous;* sometimes they are (2) *urticarial* in type; and sometimes there is (3) an outspoken dermatitis.

Conclusions. (1) Derivatives of plants belonging to the natural order *Myrtaceæ*, and especially oil of eucalyptus and myrtol, may in large doses cause profound intoxication. In certain persons there is an idiosyncrasy, the symptoms of intoxication occurring after minute or therapeutic doses. (2) The intoxication may affect chiefly the nervous system (*myrtogenic neuropathy*) or chiefly the skin (*myrtogenic dermatopathy*); in some persons, nervous and cutaneous manifestations are simultaneously observable.

(3) Recovery occurs in most instances, though several fatalities following eucalyptus poisoning have been reported.

(4) The symptoms of intoxication of the nervous system observed in man can be reproduced in animals by subcutaneous and by intraperitoneal administration of myrtol.

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A CASE OF BULIMIA, WITH REMARKS ON THE CAUSAL TREATMENT OF SOME FUNCTIONAL DISEASES

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Though bulimia is always mentioned in the proper connection, it rarely gets into indexes, and does not seem to be very frequent in practice. The descriptions in text-books are as a rule very good, but the tendency to place bulimia with polyphagia in diabetes or exophthalmic goitre must raise doubt in the mind of anyone who sees a case like the one I report, or even one who reads a current definition, as to its place in pathology. Recent studies of hunger, especially those of Cannon and Carlson and their collaborators, give an added interest to all anomalies of hunger. For these reasons and on account of the outcome of the case, I report the history of a patient sent me recently for investigation.

G. S., aged thirty-six years, architect.

Diagnosis. Bulimia, pansinusitis, acute rhinitis, pharyngitis and laryngotracheitis, caries of teeth, alveolar abscess.

Complaint. The patient has to eat more frequently and in larger quantities than normal. Hunger attacks begin with general feeling of uneasiness, followed, if food is not taken, by an intense headache, generally in the eyes or frontal region. Sometimes headache comes quickly if food is not taken, sometimes it is delayed. The patient eats from five to fifteen times in twenty-four hours. More accurately he has no regular mealtime and does not always eat with the family, but eats at any time he feels a craving. At family meals he may take a bowl of soup, crackers, rice or bread. He has acquired the habit of eating toasted bread cubes, which he always has with him in large

tin cans. He will eat a bowlful of these, or five to eight shredded wheat biscuits each time he gets hungry.

Family History. Mother and two sisters died of cancer of stomach. Father and one sister living and well. No history of tuberculosis, arthritis, constitutional or nervous disease.

Previous History. As an infant, patient had digestive disorders, according to a statement from his mother, and up to seven years had an idiosyncrasy to bananas. From seven to twenty-one he was always well. About twenty-one, while at college, he overworked, and at one time was ill two weeks with "gastritis and pleurisy." He lost weight from 175 to 135 pounds. There were then recurring attacks, following fatigue or overwork, but gradually becoming less frequent. These attacks began with a chill, followed by abdominal distention, pain through the chest, radiating to the back, causing the patient to double up. There were eructations, which seem to have suggested the name "gastritis" for the attacks. After the last attack, five years ago, the patient followed a diet composed of easily digestible food. At the age of twenty-two the right arm became paralyzed and remained so for two years, but gradually recovered. The cause was not clearly made out, though the patient was examined by several distinguished neurologists. The final opinion expressed was that the paralysis was due to sleeping on the arm.

In February, 1918, he had an infection in the head, spoken of as "grip," since which time the nose has been obstructed. The patient seemed to have been almost wholly free from subjective symptoms, and had no severe sinusitis symptoms. Later, he gave a history of "catarrh," for which the nose was treated when he was sixteen. Since then he has kept the nose clear by snuffing up salt solution. He had no idea the condition was severe and was not aware of his nasal voice. He had always led an active life, riding and walking much, playing tennis, association football and hockey. No abuse of alcohol. No history of venereal disease.

The present trouble (voracious appetite) dates from January, 1915. At first he felt hungry about 9 P.M., and would eat a bowl of rice or something similar. The condition gradually grew more severe.

Three years ago he weighed 145 pounds. He now weighs 215

pounds. In the last six weeks he has grown short of breath. When the amount of food is large the bowels are loose.

The hands have not become larger. Does not think there is any change in shape or size of head.

The present diet has been described. The amount of water consumed varies with the food, but is always more than normal. The amount of urine seems increased, but has not been measured.

The patient has been under the care of various physicians. Recently, under the view of a ductless gland disease, he was treated in turn with dried thyroid, adrenalin and pituitary preparations. The first had no effect, but the others seemed to give relief and reduced the appetite. Had also taken tincture of belladonna up to 20-drop doses. The throat got very dry and the symptoms were checked for about a day, but returned. Patient has washed out his stomach with a tube, daily for a week, with benefit. He found that bulky vegetables relieved hunger longer than meat. He can eat all kinds of food. Sometimes a small amount of food satisfies; at times he cannot eat enough.

Physical Examination (February 9, 1918). Man of large, heavy frame, well formed. Panniculus moderately thick; no abnormal fat distribution.

The skin is warm, pink or mottled when stripped in a rather cool room. Patient does not object to the cold. The lips and finger tips are slightly cyanotic. The abdomen shows white lines from the pressure of the bedclothes. Nail scratch brings out white lines, remaining several minutes. Gentle stroke with finger brings out broad white line, also lasting several minutes. The scalp hair is thin in front. Eyebrows and beard (shaved) heavy. Body hair scanty; semifeminine escutcheon.

The supra-orbital prominence, malars, nose and chin of good size, but not pathological. The voice is nasal obstructive; the nose is obstructed and shows pus in the anterior nares. The teeth are well shaped, unusually regular and not spaced. Five molar teeth are decayed to the roots. The other molars and the bicuspids are extensively repaired, but show several cavities. The gums are swollen and reveal exudate in several places. The patient explained

the bad condition of his mouth by saying he could not abstain from eating long enough to let a dentist work on him.

The tongue is not large. The posterior wall of the pharynx is covered with tenacious yellow mucopus.

The thyroid is not palpable.

Thorax broad, deep and symmetrical. Expansion good. Auscultation and percussion of lungs negative.

The heart impulse is not visible or palpable. Dulness extends $1\frac{1}{2}$ cm. to the left in the fifth interspace, $2\frac{1}{2}$ cm. to the right in the third, 2 cm. in the fourth. The first sound at the apex is impure; There is a soft blowing systolic murmur in the aortic area. Aortic second sound accentuated. The radial pulse is of good volume. Blood-pressure, 188 to 92.

The abdomen is above the level of the ribs, the wall thick and firm. Liver and spleen not palpable.

The right arm is smaller than the left, 30.5 cm. as compared with 31.5 cm. at the insertion of the deltoid. Both forearms equal; right grip weak, the thumb and index only being affected by the weakness, but with little atrophy. The right hand is paler than the left.

The reflexes are normal.

Some small hemorrhoids, otherwise rectal examination negative.

Blood: Hemoglobin, 90; red blood corpuscles, 6,600,000; leukocytes, 5600.

Wassermann tests, blood and spinal fluid negative. Five cells per cubic millimeter in the spinal fluid. Ross Jones negative.

Urine: Admission specimen, clear, light yellow. Specific gravity, 1010; acid; no sugar; no albumin. Phenolsulphonephthalein test, 10 min. trace; 1 h. 10 min., 25; 2 h. 10 min., 22; total, 47 per cent.

Blood chemistry, February 9: Non-protein nitrogen, 30.1 mg. per 100 c.c. Urea, 13.2 mg. Sugar, 0.0495 gm. per 100 c.c.

Examination of stomach contents, vomitus on passing tube. About 200 c.c.; semisolid; no mucus; no blood; HCl, 24; total acidity, 46. No lactic acid. No bacilli, yeasts or sarcines. Fat and starch present.

Test-meal, shredded wheat biscuit: Free HCl, $\frac{1}{2}$ h., 35; 1 h., 20; $1\frac{1}{2}$ h., 20; 2 h., 35; $2\frac{1}{2}$ h., 30; 3 h., 25. Total acidity, $\frac{1}{2}$ h., 55; 1 h., 60; $1\frac{1}{2}$ h., 45; 2 h., 55; $2\frac{1}{2}$ h., 40; 3 h., 40.

Stool (February 9), 410 grams, formed, dry. Large amount of shredded wheat biscuit like coarse bran; no mucus, blood or pus.

The first night the patient was in the hospital orders were left to give him anything he asked for. Between 8 P.M. and 6 A.M. he took 800 c.c. of milk; 5000 c.c. of water and 16 shredded wheat biscuits, besides some bread cubes; calories, 1684. The next twenty-four hours he took total calories, 7038.4.

These quantities of food were not considered excessive by the patient. They were lessened by the further examinations, so that we had no opportunity for seeing the possibilities in that way.

February 10. The blood examination gave non-protein nitrogen, 25 mg. per 100 c.c.; urea, 16 mg. per 100 c.c. Blood-pressure, 160 to 90. White line as before.

Sugar tolerance in blood tests: before test, 0.087; $\frac{1}{2}$ h. after, 200 grams glucose, 0.170; 1 h., 0.115; $1\frac{1}{2}$ h., 0.105; 2 h., 97; $2\frac{1}{2}$ h., 95. No sugar in urine at any time.

URINARY CONDITIONS DURING OBSERVATIONS

February	9	Amount	3800	N 9.98	NH_3N 0.863
"	10	"	4645	16.29	NH_3N 1.98
"	11	"	2900	16.40	NH_3N 2.01
"	12	"	2400	14.61	NH_3N 1.90
"	13	"	1800	14.37	NH_3N 1.78

Skiagram of head, stereoscopic, shows large frontal sinuses; posterior half of skull very thick, especially inner plate. Sella small, shallow. Appearance as of bridge of bone across top.

Films of teeth show periapical infection of two teeth and suspicious areas around several others. Referred to dentist.

Examination of nose and throat by Dr. C. A. Gundelach February 11: Left nasal chamber entirely occluded by several polyps. Right chamber filled with pus. Evident middle and superior meatus suppuration. Nasopharynx greatly infected; pharynx also. Tonsils small; submerged; chronic tonsillitis. Lingual tonsil considerably hypertrophied. Larynx and trachea show acute inflammation.

February 11. Roentgen-ray examination, gastro-intestinal, by Dr. R. W. Mills (abstract): Stomach rather atonic; is large in all dimensions; gastric tonus fairly good only; pyloric tonus fairly

good. Gastric motility no more rapid or slower than normal. No initial clearance. Cap perfect; ring perfect. At four and three-quarter hours stomach empty. Barium in terminal ileum and ascending colon. Barium enema shows cecum and entire colon of rather large dimensions; takes one-third more enema than usual. No definite evidence of colonic hypermotility. No abnormalities in or about appendix.

The patient became restless while the various tests that prohibited eating were carried on. It soon became clear that diabetes and organic stomach disease, intestinal disease and intestinal parasites and pancreatic disease could be ruled out. Pituitary disease and disease of the central nervous system seemed possible to exclude, also neurasthenia and hysteria.

The condition of the teeth and the nose and accessory cavities indicated something more than symptomatic treatment. The character of the food eaten between meals made one think of relief to reflex irritation, and the mouth and nose seemed possible sites of such irritation. I therefore advised the patient to have the local diseases treated at once, stating that this might stop the chief symptoms; if not, further investigations into metabolism were agreed to by the patient.

Work on the mouth was begun by Dr. Wm. B. Spotts, dentist in the medical service, and on the nose by Dr. Gundelach. The hopelessly defective teeth were extracted and the infections treated. The nasal polyps were removed, the largest three-quarter inch in diameter. Both antra were opened nasally and all the sphenoidal and ethmoidal sinuses and large quantities of foul pus washed out.

By March 5 the patient reported himself very much improved. "He eats three times a day, and though sometimes hungry is much less so than before. He looks well, but his voice is still somewhat nasal."

April 4. Nose almost well. No voracious appetite for a month, except once, and then not bad. No hunger at night. Feels much better in every way. Weight, 190 pounds. No white line, only a red line fading rather rapidly.

May 1. Feels well. Weight, 185 pounds. Large appetite only once since last visit; none at night.

There was no opportunity to make observations such as Carlson made with such advantage with intragastric balloons, so that we cannot tell the details of the hunger contractions. But it seems certain, from the roentgen rays as well as the clinical observations, that rapid emptying of the stomach had nothing to do with the hunger pain. Attractive as this theory of bulimia is, it seems that it must be an infrequent explanation, from negative evidence. In patients with cancer of the cardiac end of the stomach, with rapid, sometimes instantaneous emptying, hunger has not been present. My roentgenological colleague, Dr. R. W. Mills, tells me he has not seen it in any of some 25 cases of rapid emptying after gastro-enterostomy.

It is perhaps going too far to assert that the treatment was the cause of the improvement. Many will think the condition was a neurosis and the improvement a coincidence, perhaps only temporary. However that may be, I think the case has a lesson in showing the advantage of treating local diseases that may cause functional disorders rather than resorting to the narcotics, depressants or other symptomatic remedies still recommended and used in such cases.

The case illustrates another feature of therapeutics. For years medical teachers have emphasized the importance of "treating the patient and not the disease," of ascertaining the complete anatomical and functional condition of the patient and correcting all anomalies. This would seem to mean that all morbid processes should be treated, instead of treating abstract conceptions.

Focal infections, sometimes causing local symptoms, always capable of setting up other and dangerous processes, would seem to indicate careful and exhaustive treatment. And yet we see all kinds of neuroses in patients with infections of the teeth, tonsils, prostates, or appendices, but little or nothing done with the demonstrated foci unless a haphazard effort with vaccines.

DISCUSSION

Dr. Coleman said: I should like to ask Dr. Dock whether he ascertained what proportion of the large amount of food taken by the patient was utilized. It would be very interesting to know whether the toxins of the organisms infecting the teeth and sinuses had caused an increase in metabolism, without fever, but with a corresponding alteration in the patient's appetite.

ACUTE ENDOCARDITIS FOLLOWING WAR WOUNDS

Including Notes of Heart Weight and Arteriosclerosis in Soldiers

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In a previous report[1] observations on the necropsies on eighty-seven soldiers who died in active service in France were recorded, reserving for separate study certain features of the pathology of the cardiovascular system. This seemed justifiable because of the relatively large number of cases of acute endocarditis observed. It is no new fact that acute endocarditis may accompany septicemia and pyemia, but surgeons and internists often regard the soldier as resistant to such complications and neglect this possibility in their treatment of the case. The experience of the writer in France has led to the belief that treatment can be successfully modified by a consideration of the changes in myocardium and renal parenchyma which may permanently handicap the soldier in after-life. This study was taken up in the hope that light might be thrown on a subject by no means new, but as yet far from being satisfactorily explained.

As a corollary to the studies of acute endocarditis, a study of the weight of the heart is presented and also a note on the occurrence of arteriosclerosis.

Acute endocarditis was observed in fourteen of the eighty-seven necropsies. There is no assurance that a similar percentage would be seen in a larger series of cases, but data should be collected. The number is large enough to be suggestive and to direct the attention of pathologists and clinicians toward minute observation of the

valves in life and after death particularly in cases of septicemia or pyemia.

Type of Cases. Of the fourteen cases showing acute valvular lesions, twelve were pure acute disease and two showed acute lesions superimposed on preceding chronic lesions. The twelve acute cases showed involvement of the aortic valve alone in five cases; the mitral, two cases; the pulmonary, one case; the tricuspid, one case; combined mitral and aortic, three cases. One case showed chronic mitral stenosis with acute mitral and aortic lesions; one case showed chronic mitral and aortic stenosis with acute mitral lesions. The Staphylococcus pyogenes aureus was isolated in three cases, two of which were pyemias and one was a septicemia. The Streptococcus pyogenes was isolated in nine cases, two of which were pyemias and seven were septicemias. Two cases were clinically and pathologically septicemias, but were not demonstrated to be so bacteriologically. All had suffered serious primary wounds, five of which involved joints and four others of which involved other serous cavities. These wounds are irregularly distributed in regard to the valves attacked except that both the cases showing superimposition of acute or chronic lesions were penetrating wounds of the pelvis. In contrast to these figures, there were six cases of infected wounds of the joints which failed to show endocarditis, twenty-three cases of wounds of other serous cavities not including head wounds, and forty-two cases of septicemia or pyemia without noticeable lesions of the endocardium.

Average Duration of Illness. As to the duration of illness, one patient, a case of gas gangrene, succumbed in four days. The other thirteen patients were all ill one week or more; eight were ill more than two weeks; five more than three weeks; four more than four weeks, and one was ill more than five weeks. The average duration of illness was eighteen days as compared with an average of seventeen days in forty-two septic cases without endocarditis.

Type of Organism Found. All the cases were obviously either septicemia or pyemias and the Streptococcus pyogenes was the predominant organism. One case showed perfringens in the blood after death, but all the work with this organism tends to show that it is not an invader of the blood stream during life. The case in

question appeared to be septicemic as the result of pyogenic infection before the gas gangrene developed. It is not believed that Bacillus perfringens caused the acute endocarditis of this case.

Age and Term of Service. The fourteen cases, as a group, averaged twenty-nine and a half years of age and twenty-four and one-half months' service; somewhat greater in each instance than the averages for the entire group studied (twenty-seven years of age, twenty-two months' service). It may well be that the greater age and prolonged service might have reduced the resistance of these persons so as to expose them to this serious complication.

This information is summarized in Table I.

TABLE I.—SUMMARY OF THE STUDY OF CASES OF ACUTE ENDOCARDITIS IN FOURTEEN SOLDIERS

Lesions.	Case No.	Age in yrs.	Service in mos.	Illness in days.	Wound.	Disease.	Organism.
Acute aortic valvulitis	10	43	33	31	Buttock	Pyemia	Streptococcus.
	12	22	19	50	Hip-joint	Septicemia	Streptococcus.
	25	34	25	16	Thigh	Septicemia	?
	30	28	36	22	Chest	Pyemia	Streptococcus.
	51	35	15	17	Shoulder	Septicemia	Streptococcus.
Acute mitral valvulitis	7	23	22	7	Knee-joint	Septicemia	Streptococcus.
	76	20	16	10	Chest	Septicemia	Streptococcus.
Acute pulmonic valvulitis	2	22	24	29	Ankle-joint	Septicemia	Streptococcus.
Acute tricuspid valvulitis	9	29	12	28	Foot	Pyemia	Staphylococcus.
Acute mitral and aortic valvulitis	14	29	36	7	Thigh	Septicemia	Streptococcus.
	21	21	16	13	Knee- and elbow-joints	Septicemia	Streptococcus.
	40	36	18	4	Leg	Gas gangrene	Perfringens.
Acute superimposed on chronic valvulitis	20	34	35	14	Pelvis	Pyemia	Staphylococcus.
	75	37	36	8	Pelvis	Pyemia	Staphylococcus.

Note.—Streptococcus signifies a gram-positive organism in long chains. Staphylococcus signifies Staphylococcus pyogenes aureus. Pyemia indicates abscess formation in more than one organ.

Type of Lesion. The aortic lesions were in all cases extremely mild and might easily have been overlooked on less careful examination. It is of further interest that in all the aortic cases in which an organism was identified (six of the seven cases) the Streptococcus pyogenes was found, and this is true also of the acute mitral lesions. Both cases of

acute valvulitis superimposed on chronic lesions were in association with Staphylococcus pyogenes aureus. The pure aortic cases show a rather high age incidence as compared with the other cases excepting the two patients who had acute and chronic lesions. This same group of men appeared to have been in active service somewhat longer than the other cases. From the mildness of the aortic disease and the apparently long duration of illness in these cases it might be assumed that this valve is somewhat more resistant to acute disease than are the other valves, but this view is more than counterbalanced by the large number of cases in which aortic disease appeared. It can be stated, however, that whereas acute aortic disease is common, it does not become as severe and extensive as disease of the other valves, a fact in accordance with observations in civil life.

Of considerable interest is the occurrence in the 14 cases of 2 cases with valvular disease of the right side of the heart only. This is extremely uncommon in adult life, but an examination of the data in these cases shows no explanation for their occurrence.

In only one case did the acute valvulitis appear to be of undoubted embolic origin, namely, the case of acute tricuspid disease, the lesion appearing as an ulcer in the middle of the valve flap and associated with what appeared to be an abscess in the substance of the valve. The case of pulmonic disease might have had a similar origin, for at the necropsy the lesions covered the ventricular surfaces of the leaflets and might have originated as emboli in the substance of the leaflets. All the other cases appeared to originate at the line of closure. According to the work of Bayne-Jones,[2] normal vascularization of the leaflets extends to the line of closure in the auriculoventricular leaflets, but only a short distance into the semilunar leaflets. Hence, lesions of the line of closure of the semilunar leaflets probably are not of embolic origin, whereas those of the line of closure of the mitral and tricuspid leaflets may or may not be.

Chronic Valvular Lesions. There were 4 cases of chronic valvular disease without acute lesions, 2 of which were septicemias of rather short duration (five and ten days). The 2 cases of meningitis lived longer but were probably not septicemic. Of the 2 septicemic cases, 1 showed a sclerosis of the valve rather than a true chronic inflammatory process, leaving 1 case of chronic valvulitis with septicemia and without acute lesions as contrasted with 2 other cases with chronic valvulitis, pyemia and a superimposed acute lesion. This is in accord with the old view that a true chronic valvulitis predisposes to subsequent acute attacks (refer to Table II for summary).

TABLE II.—CASES OF CHRONIC VALVULAR DISEASE WITHOUT ACUTE LESIONS

Case No.	Age in yrs.	Service in mos.	Illness in days.	Valve.	Wound.	Disease.	Organism.
36	24	19	5	Sclerotic aortic	Belly	Gas gangrene	Perfringens streptococcus.
36	43	18	20	Chronic mitral	Chest	Streptococcus meningitis	No growth.
64	24	18	28	Chronic mitral	Head	Staphylococcus meningitis	?
87	29	6	10	Chronic aortic	Thigh	Septicemia	Streptococcus.

Cardiac Hypertrophy. In several of the earlier necropsies it was thought that the heart was enlarged without noticeable cause. Scales were then purchased to try to determine if the life of the soldier induces a cardiac hypertrophy. It was not possible to weigh the cadavers, so that the size was indicated as tall, medium or short; in some cases this was neglected.

The average weight of the heart in 24 men whose size was not noted was 305 gm. Excluding one heart of 420 gm. regarded as definitely hypertrophic, the average was reduced to 300 gm. Nineteen of these men had slight sclerosis of the aorta. The average service was twenty-three months and age twenty-four years. The average kidney weight was 328 gm.

The average heart weight in twenty tall men was 344 gm. Excluding two hearts of over 400 gm., this was reduced to 336 gm. Fifteen of these men had slight sclerosis of the aorta. The average service was twenty-five months and the average age twenty-eight years. The average kidney weight was 374 gm.

The average heart weight in eighteen medium sized men was 322 gm. Excluding three hearts of more than 400 gm., this was reduced to 301 gm. Thirteen of these men had slight sclerosis of the aorta. The average service was twenty months and the age twenty-eight years. The average kidney weight was 346 gm.

TABLE III.—SUMMARY OF THE STUDY AT NECROPSY OF THE HEARTS IN A SERIES OF SOLDIERS

Stature.	Number of cases.	Heart, Weight in gm.	Excluding hypertrophy.	Sclerosis.	Service.	Age.	Kidneys, Weight in gm.
No note . . .	24	305	300	19	23	24	328
Tall	20	344	336	15	25	28	374
Medium . . .	18	322	301	13	20	28	246
Small	10	265	265	5	16	24	301
Totals . . .	72	314	305	52	22	27	342

The average heart weight in ten small men was 265 gm., none exceeding 400 gm. Five of these men had slight sclerosis of the aorta. The average service was sixteen months and the age twenty-four years. The average kidney weight was 301 gm.

The foregoing information is summarized in Table III.

Influence of Arteriosclerosis and Chronic Interstitial Nephritis. The importance of the influence of arteriosclerosis and chronic interstitial nephritis was considered and the cases grouped as follows: There were 18 cases with both arteriosclerosis and chronic interstitial nephritis, whose hearts averaged 316 gm. in weight; excluding 3 cases with hearts of more than 400 gm., the average was reduced to 283 gm. There were 34 cases with arteriosclerosis and without chronic interstitial nephritis, the average heart weight being 319 gm.; excluding two large hearts, this was reduced to 314 gm. There were only 2 cases with chronic interstitial nephritis and without arteriosclerosis; too few to present figures. There were 15 cases without either arteriosclerosis or chronic interstitial nephritis, the average heart weight being 303 gm.; excluding large hearts, this was reduced to 295 gm. (Table IV shows this in summary).

TABLE IV.—SUMMARY OF THE INFLUENCE OF ARTERIOSCLEROSIS AND CHRONIC INTERSTITIAL NEPHRITIS ON HEART WEIGHTS

With arteriosclerosis and chronic interstitial nephritis.		With arteriosclerosis without chronic interstitial nephritis.		Without arteriosclerosis or chronic interstitial nephritis.	
Number of cases.	Average Weight of heart, gm.	Number of cases.	Average Weight of heart, gm.	Number of cases.	Average Weight of heart, gm.
18	316	34	319	15	303
Excluding three large hearts .	283	Excluding two large hearts . .	314	Excluding one large heart . .	295

As would be expected, the association of these two lesions is accompanied by greater heart weight than is the case when they are absent, but if the large hearts are excluded in making the average it would appear as if the arteriosclerosis were the more important change. Anatomically, the lesions were mild in both the cases of arteriosclerosis and chronic interstitial nephritis. Without functional studies of the cardiovascular system and renal sufficiency and with the variance in figures a conclusion is unjustified. No light was thrown on the variance of these figures by examining the age, service and stature of these cases, as the distribution was fairly even.

Influence of Age and Length of Service. The question of age and service was investigated, taking the average of all the cases as the dividing line. There were 36 patients more than twenty-seven years old with an

average heart weight of 326 gm., excluding five large hearts, 300 gm., in contrast to 34 patients less than twenty-seven years of age with an average heart weight of 305 gm., excluding one large heart, 301 gm. There were 34 patients with more than twenty-two months' service with an average heart weight of 350 gm., excluding three large hearts 324 gm., in contrast to 13 patients less than twenty-seven years of age and with less than twenty-two months' service, with an average heart weight of 279 gm., not including any large hearts. Table V gives a summary of these cases.

TABLE V.—SUMMARY OF THE RELATION OF AGE AND LENGTH OF SERVICE IN THEIR EFFECT ON HEART WEIGHTS

Over 27 years old	326 gm.	Under 27 years	305 gm.
Excluding five large hearts	300 gm.	Excluding one large heart	301 gm.
Over twenty-two months' service	330 gm.	Under twenty-two months' service	293 gm.
Excluding four large hearts	316 gm.	Excluding two large hearts	284 gm.
Over service and age	350 gm.	Under service and age	279 gm.
Excluding three large hearts	324 gm.	No large heart	

It will be noted that, excluding the large hearts, there is no difference in weight in the two age periods, but that under the same condition the men who have served more than twenty-two months have hearts averaging 32 gm. heavier than their fellows of shorter service. In the case of 13 men who were more than twenty-seven years of age and had more than twenty-two months of service, the hearts averaged 71 gm. greater in weight than in the case of 13 others who were less than twenty-seven years of age and had less than twenty-two months' service; excluding large hearts the difference in the two groups was 45 gm. The stature of these men was considered, but appeared to be fairly evenly distributed. It, therefore, appears that long service and increased heart weight go hand-in-hand. If to the long service there is added greater age, the increase in weight becomes more marked.

Hearts weighing 400 gm. or more have been regarded as examples of hypertrophy and deducted from the total in reaching averages. Six hearts fell in this group and all but one could be accounted for by other lesions in the body. Three of these were associated with a chronic interstitial nephritis, which although of mild degree might have been sufficiently diseased functionally to have produced heightened blood-pressure. All of these showed in addition a slight sclerosis of the aorta. One case showed the abnormality below the aortic orifice described elsewhere, which might easily have led to hypertrophy and in addition a slight sclerosis of the aorta. One other case showed only arteriosclerosis as a possible cause for the hypertrophy. One patient (Case 69) had a heart of 420 gm. with no arteriosclerosis, no valve lesion, no chronic nephritis or any other apparent cause for enlargement. His body is described as that of a "tall, heavily muscled, well-

nourished man." He had a liver of 2685 gm., showing only passive congestion, a soft, flabby spleen of 285 gm., apparently normal kidneys weighing 410 gm. He was a Scottish guardsman who had served thirty-six months.

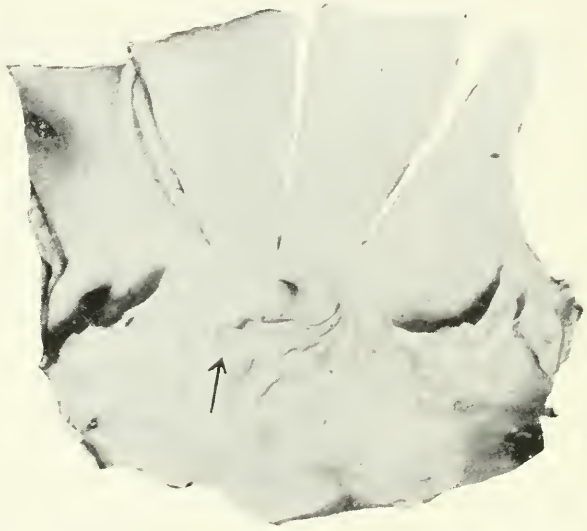

FIG. 1 (Case 21).—Aortic valve showing vegetations just above the line of closure. This case also had acute mitral disease.

FIG. 2 (Case 10).—Aortic valve showing erosion and vegetations below the corpus Arantii.

Compared with the weight of the other organs the heart is not materially enlarged and doubt is left in one's mind as to whether or not this case should be classified as a hypertrophy.

When it is noted that the greatest weight recorded in the series is 475 gm., and that next to that are two hearts of 420 gm., one of these being a doubtful hypertrophy, it can be seen that definite hypertrophy of the heart played a very small part in the gross morbid anatomy of these soldiers.

These 6 cases averaged thirty-seven years of age and twenty-seven months of service, distinctly above the average of twenty-seven years of age and twenty-two months' service. This may be taken to support the suggestion that older men of long service tend to have larger hearts than the opposite group.

Table VI gives a summary of these data.

TABLE VI.—SUMMARY OF THE FINDINGS AT NECROPSY IN SIX CASES CLASSED AS HYPERTROPHY OF HEART

Case No.	Age in yrs.	Service in mos.	Heart wt., gm.	Valve lesion.	Sclerosis aorta.	Kidney wt., gm.	Kidney lesion.	Disease.	Stature.
14	29	36	420	Acute aortic mitral valvulitis	+	430	Chronic interstitial nephritis	Streptococcus septicemia	No note.
46	26	32	410	None	+	420	Cloudy swelling	Streptococcus meningitis	Tall.
51	35	15	400	Abnormal acute aortic	+	356	Cloudy swelling	Streptococcus septicemia	Medium.
54	48	27	475	None	+	340	Chronic interstitial nephritis	Gas gangrene	Medium.
56	45	18	400	Sclerotic mitral	+	450	Chronic interstitial nephritis	Chest wounds	Medium.
69	40	36	420	None	−	410	Normal	Chest wounds perfringens	Tall.

Arteriosclerosis of the Aorta. This condition was noted in 62 of a total of 81 cases in which a note was made on the aorta. This was practically always slight, appearing usually as narrow, white, firm streaks longitudinally arranged throughout the length posteriorly, resembling a little the streaks of fatty change seen in the aortas of children dying from acute infection but being white and definitely fibrosed. A few of these showed slight fatty changes, but none showed definite calcification. It is not likely that this change can be accounted for by the acute infections from which the men died; it seems more reasonable to attribute the change to some other cause.

Coronary sclerosis was present in 5 cases, 1 of which showed also a sclerosis of the mitral valve. Sclerosis of the cerebral arteries was noted in 1 case of 77 cases examined.

Averages were estimated of the age and term of service of 62 patients who showed sclerosis of the aorta and 19 patients who failed to show it and the

resulting figures were the same in each; namely, twenty-seven years of age and twenty-two months' service. It is therefore unlikely that army service or the age of the soldier played any important part in the occurrence of the arteriosclerosis and that its cause must be sought elsewhere.

Summary and Conclusions. In summary, it may be stated that in spite of the fact that soldiers represent a group of men selected for superior physique, acute valvulitis is an important complication

Fig. 3 (Case 51).—Aortic valve showing vegetations as indicated by the upper arrow and anomaly as indicated by the lower arrow.

of septicemias and pyemias following war wounds. The men developing this complication are somewhat older and of longer service than the average of the entire group studied. The situation of the wound has little to do with this complication, except that wounds of joints form a larger percentage in the group of acute valvulitis cases than is true of the entire group. The Streptococcus pyogenes is an important organism, but is not more frequent in the smaller than in the entire group of cases. In one case embolism of

the valve vessels seems to have been a cause, and in one other it is a possible cause. The aortic leaflets are the most commonly affected and at the same time show the least marked lesions.

The weight of the heart appears to be greater in men of long service and in older men, the difference being accentuated in men when greater age and longer service coincide. It is therefore tentatively concluded that long service in the army probably leads to an increase in the weight of the heart, and that this change is more marked in men above the average age of this series of soldiers.

It cannot be demonstrated that the life of the soldier leads to the development of arteriosclerosis.

List of Cases of Acute Valvulitis

I. ACUTE AORTIC VALVULITIS

Case X (Fig. 2).—The patient, aged forty-three years, had been in the service thirty-three months. He was admitted to the casualty clearing station with shell wound of the buttock and fracture of the great trochanter. He was ill thirty-one days, a large abscess of buttocks developed and five days before death a dry pleurisy of the left side. The necropsy was performed fourteen hours after death and revealed extensive suppuration of thigh extending up to origin of psoas major but not involving hip-joint. The heart was soft and flabby with normal valves except that one aortic leaflet showed in the middle of the ventricular surface a small erosion surrounded by very minute soft white vegetations. There was also acute fibrinous pleurisy, acute purulent bronchitis, septic infarct of lung, acute splenic hyperplasia, cloudy swelling of kidneys. Direct smear from psoas muscle showed only streptococci in unusually long chains. Direct smear from septic infarct showed a mixture of organisms, the streptococcus predominating.

Case XII.—The patient, aged twenty-two years, had been in the service nineteen months. He was admitted to the casualty clearing station with shell wound of the buttock involving the sciatic nerve, with inability to extend the toes. During an illness of fifty days hemorrhage occurred, also edema of the thigh, and extensive suppuration of the thigh involving the left hip-joint and following the psoas major to within 4 cm. of the diaphragm. At necropsy, fifteen and one-half hours after death, the heart was "small, soft and flabby with pallid friable muscle; the aortic leaflets revealed numerous extremely minute soft white vegetations along the line of closure; other valves normal." There was acute fibrinous pleurisy, bronchopneu-

monia, cloudy swelling of liver, hyperplasia of splenic follicles, acute pseudomembranous colitis and acute hemorrhagic nephritis. Cultures from the heart blood showed Streptococcus pyogenes.

FIG. 4 (Case 76).—Mitral valve showing vegetation as indicated by the arrow; chordæ tendinæ enmeshed in vegetation.

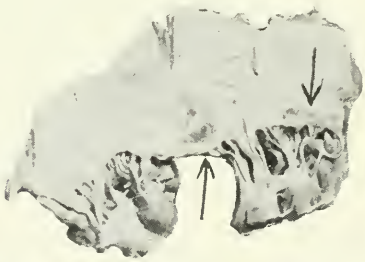

FIG. 5 (Case 20).—Mitral valve showing vegetations as indicated by the arrows.

CASE XXV.—The patient, aged thirty-four years, had been in the service twenty-five months. He was admitted to the casualty clearing station with shell wound of the hip grooving the great trochanter. During an illness of sixteen days all the symptoms of a septicemia developed. At the necropsy, four hours after death, the heart "weighed 220 gm. and was normal except for the presence of a pinhead-sized vegetation on the right posterior leaflet of the aortic valve immediately below the corpus Arantii."

There was also marked suppuration of thigh, passive congestion, edema and healed tuberculosis of lungs, cloudy swelling of the liver, submucous petechiæ of stomach, follicular and general acute splenic hyperplasia and acute nephritis. Cultures from the heart blood were contaminated.

Case XXX.—The patient, aged twenty-eight years, had been in the service thirty-six months. He was admitted to the casualty clearing station with a penetrating shell wound of chest. During an illness of twenty-two days pneumothorax developed, also hemothorax, phlebitis of right leg, purulent peritonitis, and from the chest a pure culture of Streptococcus pyogenes was obtained. At the necropsy, thirteen hours after death, the heart "weighed 345 gm., was soft and flabby and showed moderate dilatation of right side; the left posterior leaflet of the aortic valve revealed on the left half of its line of closure two pinhead-sized white fairly firm vegetations fairly well attached." There was also bilateral acute fibrinopurulent pleurisy, hypostatic pneumonia, acute purulent peritonitis (metastatic) marked cloudy swelling of liver, acute hyperplasia of spleen with multiple infected infarcts and acute nephritis. Direct smears from the right pleura and belly showed numerous long chains of gram-positive streptococci which were outgrown in cultures by contaminations. This case is regarded as a streptococcus pyemia.

Case V (Fig. 3).—The patient, aged thirty-five years, had been in the service fifteen months. Admitted to the field ambulance with extensive shell wound of left shoulder. During an illness of seventeen days gas gangrene developed, and the left upper extremity was amputated. At necropsy, seven hours after death, the heart "weighed 400 gm., showed considerable dilatation of right side, contained firm clot and frothy blood; aortic leaflets showed numerous extremely minute soft white vegetations along the line of closure; other valves normal; extending from the junction of the large mitral leaflet and left posterior aortic leaflet to a point on the septum just below the right posterior aortic leaflet was a band of fibrous tissue 2 mm. in thickness and about 15 mm. long, which widened in the middle to form a generally spherical sac about 7 mm. in diameter with an opening about 4 mm. in diameter; the septal end of this band was continued in a heavy band of muscle about 4 mm. in diameter not completely separted from the septum and extending vertically downward for 2.5 cm." The other organs showed the usual changes of gas gangrene. From the heart blood there were isolated Streptococcus pyogenes and Bacillus perfringens.

II. ACUTE MITRAL VALVULITIS

Case VII.—The patient, aged twenty-three years, had been in the service twenty-two months. He was admitted to the casualty clearing station after "lying out" four days with shell wounds of left leg, left wrist and back, without any evidence of gas gangrene. He was ill seven days and

died suddenly. The necropsy was performed eighteen hours after death and showed in addition to the wounds an acute suppurative inflammation of the left knee-joint. There was no evidence of thrombosis or embolism in the femoral veins, coronary, pulmonary or cerebral arteries. The heart was described as "somewhat soft and flabby, showing no dilatation of the left side but marked dilatation of entire right side; both sides filled with firm current jelly clot; on the posterior leaflet of the mitral valve at its line of closure were three minute, white, soft, acute vegetations." There were passive congestion of the lungs, cloudy swelling and passive congestion of the liver, acute splenic hyperplasia and acute hemorrhagic nephritis. From the knee-joint there was isolated the Streptococcus pyogenes.

Case 76 (Fig. 4).—The patient, aged twenty years, had been in the service sixteen months. He was admitted to the field ambulance with shell wound of back. At the casualty clearing station he had hematuria and vomiting; abdominal section revealed no visceral injury but retroperitoneal and intraperitoneal hemorrhage. At the base a retroperitoneal

Fig. 6 (Case 2).—Pulmonic leaflets showing massive vegetation.

abscess was opened and drained, followed by left empyema. He died after an illness of ten days. At necropsy, twenty hours after death, it was found that the wound had penetrated the lower part of chest and had split the lower pole of the left kidney. "Heart weighed 235 gm., showed a firm musculature and appeared to be normal except that the auricular surface of the right half of the posterior mitral leaflet was practically covered by a mass of small vegetations, soft, loosely adherent and salmon colored; the neighboring part of anterior leaflet showed a similar vegetation 2 mm. in diameter; other valves, coronaries and foramen ovale were normal." There was also a left-sided empyema, acute purulent bronchitis, cloudy swelling of liver and kidneys, follicular hyperplasia of spleen and wound of kidney with practically no suppuration. Cultures from the heart blood revealed pure growth Streptococcus pyogenes.

III. ACUTE PULMONARY VALVULITIS

Case 2 (Fig. 6).—The patient, aged twenty-two years, had been in the service twenty-four months. He was admitted to the casualty clearing station with shell wounds of left thigh, left ankle, left buttock and face. At the base hospital it was found that the ankle wound penetrated the ankle and tarsal joints and the thigh wound was associated with a fracture of the femur. He was ill twenty-nine days, during the course of which an abscess of left arm developed, also two abscesses of the thigh, cellulitis of the left ankle and bed-sores. The necropsy was performed twenty hours after death and the heart was described as follows: "Of about normal size, soft and flabby, shows slight general dilatation; all valves normal except the pulmonary, all three leaflets of which show on the ventricular surface extensive flat, white, soft, easily detachable vegetations covering the entire leaflet and extending slightly onto the wall of the septum, and showing three minute vegetations on the intima of the pulmonary artery." There were associated miliary abscesses of the lungs, bronchopneumonia, cloudy swelling of liver, acute splenic hyperplasia and acute nephritis. From the lung abscesses there was isolated the Streptococcus pyogenes and a staphylococcus.

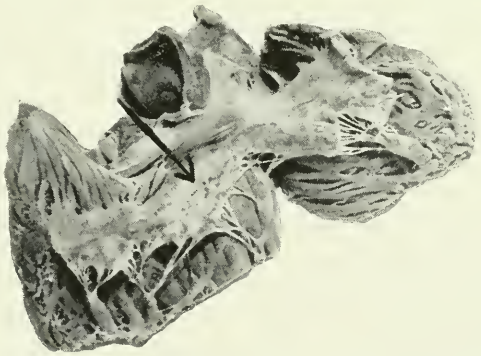

Fig. 7 (Case 9).—Tricuspid valve showing triangular ulceration in the posterior cusp.

IV. ACUTE TRICUSPID VALVULITIS

Case 9 (Fig. 7).—The patient, aged twenty-nine years, had been in the service twelve months. He was admitted to the casualty clearing station with "inflammation of connective tissue" of left foot and doubtful pleurisy of left side. At the base hospital it was found that the "inflammation of connective tissue" had followed a blister of the left instep developing on a long march. He was ill twenty-eight days, developing cellulitis of entire

left lower extremity with inguinal lymphadenitis, left subacromial bursitis and multiple subcutaneous abscesses. The necropsy was performed fourteen hours after death and revealed, in addition to the above features, acute suppurative inflammation of the ankle-joint particularly at the astragaloscaphoid junction and gangrene of the great and second toes. The heart was "soft and flabby with pallid muscle, normal valves except that the posterior leaflet of the tricuspid valve showed, near its attachment to the ring, a horizontal linear abscess 10 by 2 mm. in the substance of the valve, over which the auricular surface showed a group of minute, soft, white vegetations covering an area 4 by 5 mm." The lungs revealed one hemorrhagic infarct and a large number of small septic infarcts and abscesses, some of which are partially encapsulated, local acute fibrinous pleurisy, cloudy swelling and passive congestion of liver, acute hyperplastic splenitis, acute suppurative nephritis, occluding thrombophlebitis of left femoral veins. The heart blood showed pure culture of Staphylococcus pyogenes aureus and this organism predominated in direct smears from abscesses in lungs, kidneys, thigh wound and thrombus of vein.

V. ACUTE AORTIC AND MITRAL VALVULITIS

Case 14.—The patient, aged twenty-nine years, had been in the service thirty-six months. He was admitted to the casualty clearing station with shell wound and compound fracture of the right thigh, and superficial wounds of the leg, abdomen, chin and head. During an illness of seven days, signs of fracture of the skull and pneumonia developed. At necropsy, eleven hours after death, "the heart weighed 420 gm., showed a thick, firm left ventricle and moderately dilated right side; the mitral leaflets showed numerous small clusters of minute, white, soft, firmly attached vegetations extending along the line of closure; the aortic leaflets showed less numerous similar vegetations along the line of closure particularly marked on the left posterior leaflet." The skull showed fracture with extensive subdural hemorrhage, the lungs acute purulent bronchitis and extensive confluent bronchopneumonia, the liver cloudy swelling and fatty metamorphosis, the kidneys cloudy swelling superimposed on slight chronic interstitial nephritis. Cultures from the heart blood showed pure growth Streptococcus pyogenes.

Case 21 (Fig. 1).—The patient, aged twenty-one years, had been in the service sixteen months. He was admitted to the casualty clearing station with shell wounds penetrating right elbow-joint, right knee-joint and buttock. During an illness of thirteen days the patient developed infection of knee- and elbow-joints and finally a meningitis. At necropsy, twelve hours after death, the "heart weighed 300 gm., was markedly dilated on the right side; the aortic leaflets showed very minute, soft, white vegetations along the line of closure; the posterior leaflet of the mitral showed four such vegetations at the middle of the line of closure; left ventricular muscle was

firm, and heart was otherwise normal." There was also acute purulent cerebral meningitis, passive congestion of lungs, liver and kidneys and slight chronic interstitial nephritis. Cultures from the brain and the heart blood showed pure growth Streptococcus pyogenes.

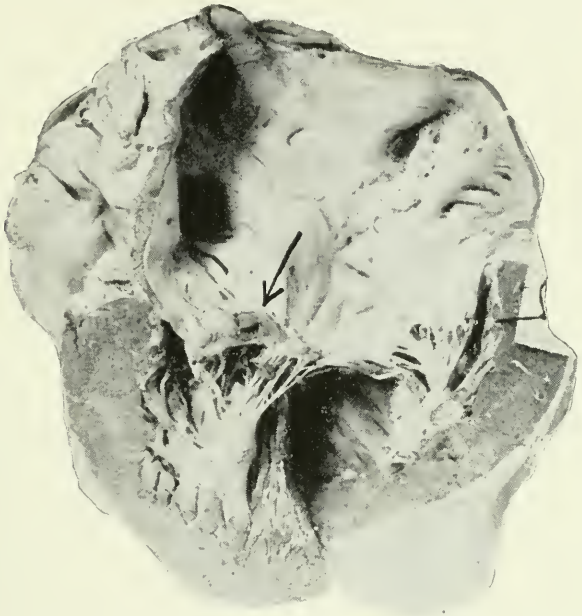

FIG. 8 (Case 75).—Mitral stenosis showing superimposed acute vegetations.

CASE 40.—The patient, aged thirty-six years, had been in the service eighteen months. He was admitted to the field ambulance with shell wound of the right leg, left knee and right arm. During an illness of four days clinical signs of a streptococcus septicemia developed, and gas gangrene of right leg for which an amputation was made in midthigh. At the necropsy, fourteen hours after death, the heart "weighed 365 gm., was of doughy consistence with epicardial congestion and hemoglobin staining of the endocardium; anterior and right posterior leaflets of aortic valve showed several red, soft, very minute vegetations on the corpora Arantii extending slightly along the lines of closure; similar vegetations were found at the right junction of the mitral leaflets approximately in the position of the line of closure." There was also gas gangrene of the right thigh with the incident softening of all the organs and a chronic interstitial nephritis. Cultures from the heart blood showed no aërobic growth; anaërobically, Bacillus perfringens was found.

VI. ACUTE SUPERIMPOSED ON CHRONIC VALVULITIS

Case 20 (Fig. 5).—The patient, aged thirty-four years, had been in the service thirty-five months. He was admitted to the casualty clearing station with shell wounds of the right buttock and left elbow. During an illness of fourteen days, there were two hemorrhages from the buttock wound and bloody stools (no perforation of the gut). At necropsy, two and a half hours after death, the "heart weighed 320 gm., and showed marked dilatation of the entire right side with slight hypertrophy of the left auricle; mitral valve showed fibrosis, adhesion, slight retraction of leaflets and adhesion with slight shortening of chordæ tendineæ; along the line of closure were numerous millimeter-sized, soft, light yellow vegetations; the stenosis was moderate, the orifice measuring 6.5 cm.; the aortic leaflets were normal except that along the line of closure of each leaflet there were a few vegetations similar to those on the mitral; valves of the right side were normal." There was, in addition, generalized icterus, acute splenic hyperplasia with multiple hemorrhagic infarcts, acute nephritis, acute fibrinopurulent pelvic peritonitis, acute pseudomembranous enterocolitis. Cultures from the heart blood showed pure growth Staphylococcus pyogenes aureus.

Case 75 (Fig. 8).—The patient, aged thirty-seven years, had been in the service thirty-six months. He was admitted to the casualty clearing station with superficial wound of chest and penetrating wound of pelvis, not involving the gut. During an illness of eight days, signs of pneumonia developed. At necropsy, four hours after death, the heart "weighed 350 gm., and showed slight hypertrophy of the left auricle; the mitral leaflets were thickened, somewhat retracted and adherent, associated with thickening and adhesion of the chordæ tendineæ; at the right junction of the leaflets on the auricular surface was a mass of dark brown, soft, firmly adherent acute vegetations 5 mm. in diameter; aortic leaflets were diffusely thickened, not retracted but showed adhesion of right posterior and anterior leaflets as far as the corpora Arantii, associated with stiffening and calcification; other valves, coronary arteries and foramen ovale were normal." There were also multiple septic infarction of the lungs, bronchopneumonia, acute fibrinous pleurisy, acute splenic hyperplasia and embolic abscesses of the kidneys. Cultures from the heart blood showed pure growth of Staphylococcus pyogenes aureus.

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PNEUMONIA AT A BASE HOSPITAL

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Early in February, a commission was sent by Surgeon-General Gorgas to Texas to study the pneumonia existing there. This commission was composed of Rufus Cole, W. G. MacCallum and Oswald T. Avery, Contract Surgeons, U. S. Army, Captains A R. Dochez and R. A. Kinsella, and Lieutenants F. G. Blake, T. M. Rivers, H. John, F. A. Stevens and Wm. C. von Glahn, Medical Reserve Corps. This special study was undertaken at the base hospital, Fort Sam Houston, San Antonio, Texas. This hospital was chosen for this work merely because pneumonia was prevailing there to a large extent at the time, and also because of its proximity to the laboratory of the Southern Department, where facilities were available for carrying out the bacteriologic and pathologic examinations. It was thought that any facts disclosed by the study there might be applicable to other camps and base hospitals. Any general application of our observations, however, must be made with reservations, for it is possible that the conditions in other hospitals may be different from those found here, and therefore that the pneumonia existing in other hospitals may differ in essential details from that present in this one.

Our preliminary survey of the cases in the hospital made it evident that not all the cases were of the same variety and that our present knowledge did not permit a ready differentiation of the cases of the different kinds. An extensive statistical study was therefore out of

the question, and we decided to make a very careful clinical, bacteriologic and pathologic study of a limited number of cases.

The study was commenced, February 1, 1918, and continued about six weeks. This paper is composed of extracts from the preliminary reports made by us to the Surgeon-General.

Part I.—Etiology and Clinical Features of the Pneumonia Occurring in the Hospital

together with notes concerning the place and mode of infection in the case of postmeasles bronchopneumonia[1]

By Rufus Cole, M.D.

Varieties of Pneumonia

The account of the results of our observations will be rendered more intelligible if we state briefly that we have found two distinct varieties of pneumonia in the wards of this hospital. First, there are present cases of acute lobar pneumonia, which are essentially identical with cases of this disease occurring in civil life. With all these cases pneumococci have been associated; second, there are present a large number of cases of bronchopneumonia, which differ essentially from the cases of the former disease in clinical features, pathology and etiology. The majority of these cases occur as complications or sequelæ of measles, though they may undoubtedly follow other infectious diseases. The pathology of these cases is carefully described by Dr. MacCallum in his report. The etiologic agent in all the cases studied here has appeared to be a streptococcus producing lysis of red blood corpuscles when grown on a medium containing blood. Similar observations have also been made in other Army hospitals, and it seems probable that these streptococci are responsible for most of the bronchopneumonia occurring in the present epidemic of measles. Previous observations, however, suggest that other bacteria may also be responsible for cases with similar clinical and pathologic features. In the further discussion,

[1] This part of the work was carried out with the assistance of Oswald T. Avery, A. R. Dochez, R. A. Kinsella, F. G. Blake, T. M. Rivers, H. John, and F. A. Stevens.

we shall refer to these two varieties of pneumonia as "acute lobar pneumonia" and "bronchopneumonia." Finally, there occurs, in no inconsiderable number of patients, a combination of these two types of disease, or infection with both pneumococci and streptococci. In these cases, one or the other of the two varieties of disease is probably primary, secondary infection later occurring with the subsequent development of the other variety.

Since the regular hospital data were not considered sufficient for our purposes, complete histories were obtained from a series of cases of both varieties, and our own physical examinations were made and the results carefully recorded. Thirty cases of bronchopneumonia, thirty-two cases of acute lobar pneumonia, and nine cases in which the two varieties of infection were present have been studied.

It was impossible to study all of the cases of pneumonia in the hospital in this way. Consequently, in a considerable number of cases coming to necropsy, the clinical data are slight. On the other hand, many of the cases studied by us ended in recovery, and consequently the pathologic lesions present can only be inferred from the knowledge obtained in the other cases in which necropsy was performed. In twelve cases of bronchopneumonia, however, the clinical observations could be correlated with the pathologic findings.

Bronchopneumonia. *Bacteriology.* The evidence that S. hemolyticus is the etiologic agent in these cases is given by the study of cultures made from the blood during life and from the organs and tissues of the body after death, and by the study of the sputum coughed directly from the lung.

Cultures from the blood during life were made in fifteen cases. In only two cases was a growth obtained. In these cases a pure growth of S. hemolyticus occurred. The cultures were made only within twenty-four hours of death, however. Studies of the bacteria present in specimens of sputum expectorated from the lung were made in all the cases. The method employed was practically that described previously for the study of the sputum in lobar pneumonia.

Specimens of sputum directly coughed from the lung were obtained in sterile containers. After the washing of portions of this sputum, cultures were made on the surface of blood agar plates, and a small portion of sputum was injected into a mouse. After the

death of the mouse, the peritoneal exudate was examined microscopically, and cultures were made from this exudate and from the heart's blood.

In all the cases that we have classified as bronchopneumonia, the cultures from the sputum on blood agar plates showed the presence of S. hemolyticus in large numbers. In most of the cases in which the mouse test was carried out, examination of the heart's blood showed the presence of this organism (in sixteen out of seventeen cases). In thirteen of the specimens of sputum, B. influenzæ as well as S. hemolyticus was found on the plates. In five instances, the patients died and came to necropsy, and in these instances B. influenzæ was also present in the affected lungs. In eight instances, B. influenzæ was also present in the heart's blood of the mouse. Whether this organism plays any part in this disease is not known. Its very frequent presence is of much interest.

Cultures were made from the infected areas in the lungs, the heart's blood, the pleura, the pericardium, and frequently from other organs of the patients coming to necropsy. In making cultures from the lungs, the pleura over the infected area was seared with a hot knife, and a cone-shaped piece of the lung was removed with sterile instruments. Cultures and smears were then made from the tip of the portion removed. In all of the cases diagnosed as bronchopneumonia during life and all of those cases coming to necropsy which showed the presence of the lesions described by Dr. MacCallum as interstitial bronchopneumonia, S. hemolyticus was found to be present in the affected portion of the lung, usually in pure culture. In most of the cases in which empyema occurred, these organisms were present in the fluid in pure cultures.

It was also the rule to find these organisms in the heart's blood after death. In a few cases influenza bacilli were also present in the blood and tissues, along with S. hemolyticus. These cases, however, did not differ from those in which the streptococcus was present alone.

Clinical Course. The picture of the clinical course of the disease which can be constructed from our data is necessarily incomplete and posibly incorrect in certain details. It is hoped, however, that it may be amplified and corrected by more complete studies in

other camps. The study of these cases has not made it possible to differentiate, clinically, between the cases showing the lesions described by Dr. MacCallum as interstitial bronchopneumonia, and those showing the lesions described by him as lobular pneumonia. Consequently in our discussion all these cases are termed "bronchopneumonia."

Onset. All the cases of this group have followed measles. In seven of our thirty cases, a history was obtained of a chronic cough, coryza or sore throat previous to the appearance of the symptoms of measles. Whether pneumonia is more likely to occur in those men who have had previous infections of the respiratory tract is not certain, but it is possible that this factor is of some, but not paramount, importance.

A considerable number of cases of measles show laryngeal infection, as shown by the occurrence of hoarseness and huskiness of the voice. That this is a true inflammatory lesion is shown by the fact that minute ulcerations may be present on the vocal cords.

The first definite symptoms of the disease are usually cough, fever, slight respiratory distress, and the expectoration of a mucopurulent sputum. All of these symptoms, as is known, usually occur in some degree during the febrile stage of measles. In certain cases of measles the temperature does not fall with, or shortly after, the appearance of the rash, as is usually the case, but the fever continues and becomes higher and the symptoms mentioned increase in severity. In other cases the temperature falls to normal, and then after a period of from a few days to three weeks the temperature again becomes elevated and the symptoms mentioned become severe and characteristic of the disease. In none of the cases we have seen, however, nor in any of those of which we have histories, has there been a complete disappearance of all the symptoms referable to the respiratory tract during the interval between recovery from measles and onset of bronchopneumonia. Even in the cases in which the onset has occurred following the discharge of the patient from the hospital, it is quite certain that cough or respiratory difficulty was present at the time of discharge and persisted up to the time of onset of the pneumonia.

In all the cases that we have observed, the onset has been gradual.

In no case was there a chill with sudden elevation of temperature. Vomiting during the early period has been rare.

These observations, as well as the pathologic studies, indicate that the infection, as well as the lesion, is probably a descending one, and that no sharp line can be drawn either in time or symptoms, between the occurrence of the pharyngitis, laryngitis, bronchitis, and finally the bronchiolitis and bronchopneumonia.

Symptoms. When the disease is well developed, the following are the common symptoms:

Fever: Usually the fever is not high, rarely going higher than 104° F., and even in the uncomplicated cases the temperature is frequently irregular. Wide diurnal sweeps of the temperature curve, however, have usually been associated with the presence of empyema.

Pulse: The pulse has not been extremely rapid, even in the cases near death. Special attention has not been given to the occurrence of irregularities.

Respiratory Distress: This is the most marked and characteristic symptom of the disease, and is usually present even in the early stages. This is quite distinct from the respiratory difficulty seen in acute lobar pneumonia, with the expiratory grunt. In bronchopneumonia the great difficulty is with inspiration, the accessory muscle then being strongly brought into action. Frequently the expansion of the chest wall is slight, but the diaphragmatic pull is powerful, the costal margin being drawn on, and the intracostal spaces being markedly retracted with each inspiration. The patients seem consciously to have difficulty in getting sufficient air into the chest, but the inspiratory phase is not prolonged. The respiratory rate is usually not extremely rapid; frequently, even in very ill patients, the rate is not over thirty per minute.

Cyanosis: This is practically always present, even in the early stages, and in the more severe cases becomes extreme.

Cough: The cough is troublesome; frequently it is markedly increased by change in posture.

Sputum: Usually the expectoration is fairly free and moderate in amount. Its character varies markedly in the different cases and in the different stages of the disease. Early in our studies it was thought that the sputum had a specific appearance, being light-greenish, mucopurulent, sometimes somewhat blood streaked, and of a homogeneous character, spreading like molasses over the bottom of a cup. Later, however, typical cases have been observed in which this kind of sputum was never seen. In some cases the sputum has been nummular, quite mucoid, the masses being tenacious and somewhat sticky. In other cases the nummular masses have been

greenish and very purulent. In none of the uncomplicated cases has the sputum been sticky and of a rusty color like that seen in acute lobar pneumonia, nor has it contained large amounts of bright-red blood, as is sometimes seen in the early stages of lobar pneumonia. Whatever its character, it practically always contains large numbers of pus cells.

Restlessness: This is a striking feature of the condition. The patients are fairly alert, rarely delirious, but always anxious and frequently frightened. Sleeeplessness, probably due largely to the cough and respiratory difficulty, is very frequently present.

Pain: This is frequently one of the symptoms, and is due to the pleurisy which is almost invariably present. Abdominal pain, in the uncomplicated cases, has not been frequent in this series.

In the typical cases, the symptoms we have mentioned are quite striking and more or less characteristic. It must be remembered, however, that similar symptoms, though of milder grade, are also present in cases of bronchitis without involvement of the smaller bronchioles. The symptoms are characteristic enough in the severe cases, however, to differentiate them from cases of acute lobar pneumonia.

Signs. We have already spoken of the obvious signs of respiratory distress and the cyanosis which is so striking. Physical examination of the chest may or may not reveal signs indicating consolidation. This, of course, depends on the intensity and focal distribution of the lesions. Where the process is very diffuse, the chest may be resonant throughout on percussion, though in certain regions, especially at the bases, the percussion note is frequently impaired. On auscultation, rales are usually heard throughout the chest. There are frequently musical and squeaking, in addition to moist, crackling, rales. In typical cases, the rales are more numerous during inspiration, and the inspiratory murmur is harsh. In such cases, the expiratory murmur may be scarcely audible; even though the expiratory murmur is inaudible, however, a succession of medium, moist rales may be heard during the expiratory phase. Over the areas of impaired resonance the breath-sounds may be very faint or absent until after the patient coughs, when harsh, mucous rales are heard, and the breath sounds become audible.

In some cases characteristic signs of consolidation, impaired resonance, tubular breathing and intensified spoken and whispered

voice sounds are present over small areas. Frequently these signs persist for a few days, and then entirely disappear. In our early cases, these signs were most confusing and difficult to interpret. As we became better acquainted with the pathologic lesions, however, the meaning became obvious. I shall not attempt to bring the signs into relation with the lesions, since this relation becomes quite clear on the reading of Dr. MacCallum's report.

In no uncomplicated cases have we seen wide areas of dulness with characteristic tubular breathing and other signs of consolidation. When these signs have been present, there was always a complicating lobar pneumonia. In a few cases, however, later in the disease, there has been impairment of the percussion note over a wide area, with quite distant tubular breathing over this area, but with voice sounds fairly well transmitted. The repeated insertion of a needle in these cases has failed to reveal fluid, and the needle has felt as though it were in a more or less solid lung. We have interpreted these signs as due to a quite widespread involvement of the lung, with a marked degree of proliferation and plugging of the bronchi, as described by Dr. MacCallum. These are probably the cases which go on to necrosis and abscess formation, such as was seen in three of the necropsy cases. It must be remembered, however, that in the only cases of this type that we have seen at necropsy there was a marked accumulation of fluid in the pleura.

Complications. Focal infections, such as tonsillitis and otitis media, may be present. They have not occurred frequently in this series, however. The most important complication is empyema.

Empyema. This condition occurs with great frequency, being present in sixteen of the thirty cases, and in all but one of the necropsy cases. In ten of the cases, the condition was diagnosed by aspiration of fluid from the chest during life. In four additional cases, fluid was obtained from the chest on aspiration, but in these cases, the fluid was only slightly turbid, and contained no bacteria demonstrable by culture.

The diagnosis of the presence of fluid or pus in the pleural cavity in these cases is frequently difficult. In the cases in which large accumulations of fluid have occurred, no great skill is required. It is probably of great importance, however, to detect the presence of

small amounts of fluid, and to do this as early after the fluid appears as possible. Small amounts of fluid can be detected only by employing the methods of physical examination of the chest. Roentgen examination is of assistance in certain cases. We have already stated that occasionally, over the more intensely affected areas, there is dulness on percussion, and the breath-sounds may be distant. To determine whether these signs are due to an intrapulmonary lesion or to the accumulation of fluid in the pleural cavity is frequently very difficult. The greater intensity of the dulness on percussion, when fluid is present, and the distant faint tubular breathing heard at the margin of the area, are the signs of greater importance. Fortunately, the decision can be obtained by insertion of a needle, and in doubtful cases, this may be done not only once, but many times, if necessary.

Character of the Fluid: In most of our cases, the fluid obtained has been thin, but turbid, owing to the presence of bacteria and numerous fibrinous, purulent floccules. In only three or four cases has a thick, greenish-yellow pus been encountered. The infrequency of an exudate of this character should lead one to suspect, when such fluid is found, that the condition is a complication of lobar pneumonia and not of bronchopneumonia.

Mortality. Of the thirty patients studied by us, fourteen died and sixteen recovered, a mortality of 47 per cent. Several of the patients are still very ill, however, and will probably die. Since the cases were not taken in succession, it is impossible to say whether or not this is a fair estimate of the mortality rate. Probably the percentage of cases ending fatally in this hospital has been considerably higher than this. A most striking fact is that all the necropsy cases in our series were complicated by empyema. In many cases it has seemed that death was related directly to this complication.

Treatment. No observations were made on the effect of any special form of treatment. Since the occurrence of empyema is an important factor in the outcome of the treatment of this complication, it deserves a few words of discussion.

Seven of the empyema patients were operated on, a rib resection with drainage being performed in each case. Of these patients, four

have died. All of the others are very sick, and a fatal outcome is probable in one or more. On the other hand, of four patients in whom fluid containing streptococci was aspirated from the chest and operation was not performed, all have died. There were three cases in which fluid containing a moderate number of pus cells but no bacteria was aspirated from the chest. One of these patients was operated on; the other two were not. All three of these patients have lived, and from present indications will probably recover, though the patient operated on is still very ill. Our observations are not sufficient to enable us to draw any conclusions as to operation in this condition. They suggest, however, that in the cases in which fluid containing streptococci is aspirated from the lung, the chest should be opened and drained. But the question of operation in these cases is a difficult one, and we cannot be guided entirely by our experience with empyema complicating lobar pneumonia. The problem deserves special study.

Lobar Pneumonia. During the course of our study of cases of bronchopneumonia, a considerable number of cases of typical lobar pneumonia were encountered. Some of these were chosen for study deliberately in order to have a control for the other work; in some the differential diagnosis was made only after careful investigation. One purpose of this study was to demonstrate to the hospital and laboratory personnel the fact that, under the conditions existing here, rapid and accurate diagnosis of the type of pneumococcus causing the infection in lobar pneumobia could be made. A small number of the patients were treated with serum by us or under our direction. This was also done for the purpose of demonstration.

Thirty-two cases of lobar pneumonia were studied. Only two of these patients had recently had measles: one one month, and the other six weeks previous to onset. There seemed no definite relation between the measles and pneumonia in these cases. In one other case not included in this series, an apparent pulmonary infection with pneumococcus Type IV occurred during convalescence from measles. There was a pleural exudation of clear, sterile fluid; but the signs of lobar pneumonia were never definite.

Of these cases, seventeen were associated with Type I pneumo-

coccus in the sputum; three with Type II; four with atypical Type II; one with Type III; six with Type IV, and one with S. mucosus.

The etiologic diagnosis was made within twenty-four hours in all these cases except two. In these cases, the delay was due to the fact that the sputum was very scanty and unsatisfactory, and the tests had to be repeated. The examination in both of these cases was made late in the disease. (Some of the patients were studied on admission, others only after they had been in the wards for some days.) In seventeen cases, the diagnosis was made within eight hours, the Avery medium being employed. Considering the conditions under which we worked, this result seems quite satisfactory and demonstrates the possibility of type determinations in a military hospital.

In eleven cases, the presence of fluid in the chest was determined by aspiration. In five cases the fluid was clear, or very slightly turbid. In four of these cases the fluid was sterile; in the remaining case the fluid was contaminated after removal from the chest and cultures could not be made. In these five cases, the fluid was removed by aspiration, and all the patients recovered without operation. In five other cases, the fluid was very turbid, and cultures revealed the presence of pneumococcus Type I. All of these patients were drained. Three of them are now well or are satisfactorily convalescing. Two of them are still very ill and have irregular fever. In the remaining case the fluid was thick and green, and cultures showed the presence of pneumococcus Type II. This patient was operated on and is also convalescing.

In eight of the Type I cases, the patients were treated with serum. Two of the treated patients were found to be sensitive to horse serum, and it was necessary to desensitize them before the administration of large amounts of serum. All but one recovered promptly; this one developed empyema. This patient has done well since operation and is now convalescent. The results of this small series of cases, therefore, were satisfactory.

Of the thirty-two patients, two died; two of the empyema patients are still ill, and the result is in doubt. The others have recovered.

This experience with lobar pneumonia in this hospital leads us to believe that it does not differ essentially from that seen in civil

hospitals, except, perhaps, in its relative mildness. This, however, is to be expected in a population composed of healthy young adults.

Cases of Mixed Infection or Doubtful Cases. In addition to the cases which were clinically identified as bronchopneumonia and which at necropsy were found to show the lesions described as interstitial bronchopneumonia or lobular pneumonia, and the cases which were typically lobar pneumonia, both clinically and at necropsy, there occurred a series of cases which were more or less complex in their clinical, etiologic and pathologic features.

There were seven cases in which evidence was obtained of a mixed infection with pneumococcus and S. hemolyticus, the infections being present simultaneously or in succession. Four of these cases were in patients who had recently had measles:

The first patient had signs of bronchopneumonia beginning a few days after measles. Four days later there was an acute exacerbation of symptoms with signs resembling pneumonia. This patient developed empyema on the side of the lobar involvement; and from this fluid during life pneumococcus Type IV was obtained. Death came six days after the onset of the severe symptom. The necropsy showed the presence of lobar pneumonia of the left lower lobe and an area of typical bronchopneumonia in other portions of the lung. From the blood and the right lung, S. hemolyticus was isolated. From the pleural exudate both S. hemolyticus and pneumococcus Type IV were cultivated. That a combined infection in this case was present is certain. The chronologic course of events is more difficult to decide. It is impossible to say definitely whether the patient had a bronchopneumonia, with secondary pneumococcus infection, which led to septicemia and death, or whether the streptococcus infection occurred later, or finally whether the two infections occurred simultaneously.

The second patient had otitis media and also pulmonary symptoms lasting almost a month following measles. There then occurred an exacerbation of signs and symptoms, and the ward surgeon made a diagnosis of pneumonia. We saw him two days later and found an empyema on the left side, in addition to some signs of consolidation of the left lower lobe. The fluid from the chest contained S. hemolyticus, but the blood culture showed the presence of pneumococcus Type IV. The patient died two days later, and at necropsy a true lobar pneumonia was present, but no evidences of bronchopneumonia. In the cultures at necropsy, only S. hemolyticus was obtained from both lungs, and S. hemolyticus and B. influenzæ from the blood. This case is difficult to interpret. The patient had a lobar pneumonia, and this was probably due to pneumococcus Type IV, although

for some unexplained reason these organisms were not found at necropsy. Whether the streptococcus infection occurred early in the illness or only shortly before death cannot be determined. Unfortunately, the early clinical notes are incomplete, and we have no knowledge of the severity of the early lung involvement.

The third patient developed fever and respiratory symptoms ten days after an attack of measles. In the interval, however, he had had slight, irregular fever. We saw him four days later. He had then only signs of diffuse lung involvement, with indications of empyema on the left side. The sputum contained S. hemolyticus, as did also the purulent fluid aspirated from the chest. No pneumococci were isolated. Four days later he was operated on, and the pleural cavity was drained. He lived almost two weeks, and then died. At necropsy an undrained pocket of pus was found between the left lung and the pericardium, and in addition there was almost complete uniform consolidation of the entire left lung. The other lung showed no evidences of bronchopneumonia. At necropsy, S. hemolyticus was found in all the cultures, as well as a gram-negative bacillus producing a putrefactive odor. In this case lobar pneumonia existed, without the presence of pneumococci being demonstrated at any time. This may have been due, however, to the overgrowth of the culture with a putrefactive organism, which was undoubtedly a terminal invader. When the lobar pneumonia began, or whether bronchopneumonia was ever present, cannot, of course, be decided.

The fourth patient developed typical lobar pneumonia during convalescence from measles. The blood culture showed the presence of pneumococcus Type I. He developed fluid in the left chest which was purulent, and contained pneumococcus Type I and S. hemolyticus. He died three days after the tapping, and at necropsy no pneumonia was found, but several small abscesses in the left lung and a very large amount of purulent exudate in the left pleura. The necropsy culture showed only the presence of streptococci. No pneumococci grew.

There were three patients suffering from acute lobar pneumonia in the pneumonia wards who gave no history of measles but in whom evidence of additional infection with S. hemolyticus was obtained. In two of these cases the pneumococcus causing the lobar pneumonia was Type II; in one, Type I.

One of these patients, during convalescence from pneumonia due to pneumococcus Type II, developed empyema, and the pleural exudate contained S. hemolyticus and B. influenzæ. He had had some cough and sore-throat for three weeks before the onset of pneumonia, and it is possible that the streptococcus infection antedated the pneumonia. There is no definite evidence for this, however.

The second patient had quite a typical attack of acute lobar pneumonia, also due to pneumococcus Type II. He gave no history of any pulmonary symptoms previous to the onset of pneumonia. During convalescence, he developed an irregular fever and signs of scattered lesions in the chest. There occurred an effusion of fluid in the pleura, cultures from which were sterile. The examination of the sputum at this time, however, revealed the presence of S. hemolyticus, which had previously been absent. In spite of the fact that the chest fluid was sterile, the chest was opened and drained. The signs of diffuse involvement of the lungs, however, continued and the patient, one week after operation, is still seriously ill. The study of this case is incomplete, and the evidence of secondary streptococcus infection is not satisfactory, but is suggestive.

The third patient suffered from acute lobar pneumonia, due to pneumococcus Type I, involving the right lower lobe. Convalescence was normal for a week. Signs of pulmonary involvement persisted, however. At the end of the week, the temperature again became elevated, and the presence of fluid in the chest was suspected. Repeated insertion of a needle, however, failed to reveal fluid. The sputum, however, changed in character, and examination now showed the presence of S. hemolyticus and B. influenzæ. Finally, about two weeks after the second onset of fever, a small amount of dark, foul-smelling fluid was obtained by puncture, apparently from the lung. This showed the presence of S. hemolyticus and the staphylococcus. About a week later the chest was opened and a lung abscess was drained. Whether the occurrence of abscess was due to secondary infection with streptococci or whether this infection was secondary to the abscess formation is, of course, not certain.

There were two additional patients seen by us in the pneumonia ward who developed empyema, with S. hemolyticus in the fluid. One patient had never had measles and the other had had measles two weeks previously. In the case without measles, the occurrence of pneumonia was doubtful.

This patient had been slightly ill for two weeks previous to admission, but had been performing his duties. The pleural effusion was present on admission, so infection occurred outside the hospital. The sputum contained S. hemolyticus and B. influenzæ, and the pleural fluid contained S. hemolyticus. The patient was operated on and recovered.

In the second case, which followed measles, there were signs of lobar pneumonia with empyema. The sputum contained only S. hemolyticus and B. influenzæ. The pleural exudate contained S. hemolyticus. The patient was operated on, and his present condition is fairly favorable. It is possible that this patient had bronchopneumonia, and not lobar pneumonia.

These cases indicate the frequency of complicated pulmonary infections in the present epidemic, and they also show the difficulty of interpreting the course of events in certain cases. It is true that in most of these cases no careful observations were made during the early stages of the illness. It seems quite certain that lobar pneumonia may sometimes occur in patients already infected with streptococci and with bronchopneumonia already present in the lungs. That bronchopneumonia occurs secondarily to lobar pneumonia is not so well shown by our cases; but they do show that in cases of lobar pneumonia, secondary infection with streptococci not infrequently occurs. This is obviously of much practical importance, suggesting that, so far as possible, patients with lobar pneumonia should be protected from infection with this streptococcus.

Place and Mode of Infection in Post Measles Bronchopneumonia. From the data previously presented, there appears little doubt that a hemolytic streptococcus is the chief, if not the only, cause of the bronchopneumonia following measles which occurs among the soldiers at this post.

We have previously indicated that the infection in these cases is probably descending, occurring first in the throat, and successively involving the lower respiratory passages, and finally the lung. It therefore became of much interest and practical importance to learn whether hemolytic streptococci are present in the upper respiratory tract of all measles patients, and, if so, at what stage of the disease they are first present, or, on the other hand, whether these bacteria are present only in the throats of these patients who later develop pulmonary lesions.

We therefore first attempted to determine the prevalence of hemolytic streptococci in the throats of all the patients in the measles wards of this hospital. To do this, cultures were made from the pharynx and tonsils of these patients on blood-agar plates. The plates were incubated twenty-four hours and then studied for the presence of hemolyzing streptococci. These organisms were identified by isolation in pure culture from a single colony and by testing staining reaction, morphology, cultural characteristics, bile solubility, hemolytic activity and fermentation reactions. Hemolysis was determined by testing the power of a twenty-four-hour broth culture

to hemolyze an equal amount of a 5 per cent. suspension of the red blood cells of rabbits. The degree of hemolysis was recorded at the end of two hours at 37° C. Table I gives the results of the study.

TABLE 1.—INCIDENCE OF STREPTOCOCCUS HEMOLYTICUS IN THROAT OF PATIENTS IN MEASLES WARDS

Total number of cases examined.	Number of positive cases.	Number of negative cases.	Per cent. of positive cases.
69	39	30	56.5

At the time of the examination, these patients had been in the measles wards for periods of time varying from one to fifty-five days. Of the sixty-nine patients examined, thirty-nine, or 56.5 per cent., showed the presence of S. hemolyticus in the throat.

These observations indicate that a large proportion of the patients confined to the measles wards harbor these organisms in the throat.

It next appeared of importance to learn whether or not this high incidence of carriers of hemolytic streptococci is peculiar to the measles wards or whether a similar state of affairs exists among the patients in other wards of the hospital. The incidence of streptococci of this variety in the throats of normal individuals under ordinary circumstances has not been determined accurately. In the presence of an epidemic of streptococcus infection, such as streptococcic sore-throat, it has been found that a considerable number of healthy persons may carry this organism in the throat. On the other hand, the observers who have made fairly extensive studies on the flora of the normal throat, in the absence of epidemics of this kind, report that the occurrence of actively hemolytic streptococci in the throats is very rare. At the time of our arrival at San Antonio, it was evident that an epidemic of coryza, laryngitis and mild bronchitis existed among both the civil and the military population. In some limited observations which we made, it was found that in the throats of persons suffering from this affection, hemolytic streptococci and also influenza bacilli were occasionally present, singly or combined. It was possible, therefore, that the study of persons other than those suffering from measles might show a high incidence of hemolytic streptococci in the throats. Consequently, cultures were made from the throats of patients in a ward in which the patients

were suspected of having tuberculosis but who had no other disease. Table II presents the results of this study.

TABLE II.—OCCURRENCE OF STREPTOCOCCUS HEMOLYTICUS IN THE THROATS OF TUBERCULOSIS SUSPECTS (WARD 27)

Total number of cases examined.	Number of positive cases.	Number of negative cases.	Per cent. of positive cases.
28	6	22	21.4

The occurrence of S. hemolyticus in the throats of these patients is considerably less than the incidence among the measles patients. It should be mentioned that the patients in the tuberculosis ward are not rigidly isolated from patients in other parts of the hospital, transfers from this ward to another, and *vice versa*, not infrequently being made. Several cases of tonsillitis and pharyngitis were discovered during the process of making cultures. Moreover, these patients live in very close association, being confined in the ward and only a few of them being confined to bed.

There were two methods available to discover whether the measles patients acquired the hemolytic streptococci before admission, or whether transfer from one patient to another probably occurred in the ward. One method was to make cultures on a large number of men in the barracks from which the patients with measles came, with the object of learning whether the incidence of streptococci in the throats of these healthy men was less than that among the men in the wards; the other was to make cultures from the patients with measles on admission to the hospital and then to repeat the examinations from time to time, in order to learn whether or not any of the patients with negative cultures later acquired the organisms. The latter method was chosen as consuming less time and more likely to give definite information. The results of the study are presented in Table III.

TABLE III.—OCCURRENCE OF STREPTOCOCCUS HEMOLYTICUS IN THE THROATS OF MEASLES PATIENTS ON ADMISSION AND THE SUBSEQUENT ACQUISITION OF THE ORGANISM IN THE CASES PREVIOUSLY NEGATIVE

		Per cent.
Total number of cases examined	44	
Number of cases positive on admission	5	11.4
Number of cases positive three to five days after admission	17	38.6
Number of cases on final examination—eight to sixteen days after admission	25	56.8

An analysis of this table indicates that a relatively small percentage of patients on admission to the measles wards harbor S. hemolyticus in their throats. However, as the time of residence in the ward increases, the number of carriers of S. hemolyticus increases, until finally the percentage of incidence becomes as high as that found in the measles wards in general. Because of these observations, there seems to be very little reason to doubt that a large percentage of measles patients acquire S. hemolyticus in their throats for the first time during their stay in the hospital wards.

While this study is not extensive enough to be absolutely conclusive, it indicates strongly that the high incidence of bronchopneumonia during convalescence from measles is directly related to the transfer of the infectious agent from one patient to another in the wards of the hospital.

These observations led us to suspect that the frequent occurrence of streptococcus complications, especially empyema, might also be related to the possible wide distribution of hemolytic streptococci among the patients in the pneumonia wards. Although an effort has been made to admit to the wards assigned to the care of patients suffering from acute lobar pneumonia only patients suffering from this disease, it is quite certain that owing to the difficulties of diagnosis, a considerable number of patients with bronchopneumonia have been treated in these wards. We have already referred to certain of these cases.

To investigate this question, cultures were made from the throats of all the patients in two wards which contained only patients thought to have acute lobar pneumonia. Cultures were made from forty-five patients. The technic employed was exactly that used in the tests previously mentioned. It was found that twenty-six, or 57.7 per cent., of all these patients harbored hemolytic streptococci. In view of the high incidence of streptococcus infections among the lobar pneumonia patients, these results are most interesting and suggestive. There is no reason to believe that the percentage of patients carrying hemolytic streptococci on admission is larger than the percentage of measles patients who do so when admitted. This question, however, has not been investigated.

Comment and Conclusions. The studies indicate that the cases of pneumonia at the base hospital, Fort Sam Houston, are chiefly of two varieties: first, acute lobar pneumonia, which does not differ essentially from that which occurs elsewhere; and second, bronchopneumonia, which in most cases, at present at least, follows measles.

The pulmonary lesions in most cases of this type of bronchopneumonia are characteristic and specific and have been studied and described by Dr. MacCallum. The etiologic agent in all the cases studied by us has been S. hemolyticus. There is no evidence presented by this work that indicates that pneumococcus causes the lesions and symptoms of this condition. Pneumonia following measles may be due to pneumococci, but the pulmonary lesion is then of the lobar variety. This complication of measles, however, is comparatively rare. Cases may occur in which both types of infection and both types of lesions are present. The sequence of events in such cases is difficult to determine and is probably not always the same.

Streptococcus infections following lobar pneumonia occur with considerable frequency in this hospital. Bronchopneumonia similar to that following measles may also probably occur as a sequel of acute lobar pneumonia, though the evidence for this is not conclusive. Whether in the cases of streptococcus empyema, complicating lobar pneumonia, pulmonary lesions due to the streptococci are always present or not, has not been determined.

The mortality in the cases of bronchopneumonia is very high; that of uncomplicated lobar pneumonia is low. Practically all the fatal cases of bronchopneumonia are complicated by empyema. The incidence of empyema among the uncomplicated cases of lobar pneumonia does not seem to be extremely high.

Our observations indicate that the number of measles patients harboring hemolytic streptococci on admission to the hospital is not large. The majority of the patients with measles acquire this organism during their stay in the hospital. The chance of developing postmeasles streptococcus infections is therefore increased by residence in this hospital.

A very large number of the patients suffering from acute lobar

pneumonia have hemolytic streptococci in their throats. We have no direct evidence that they acquire these bacteria in the hospital, but that presumptive evidence indicates that many of them do so.

The work indicates that the high incidence of pneumonia in this hospital and the resulting high mortality have been due, to some extent at least, to infection occurring within the hospital itself. The conditions are not unlike those surrounding puerperal fever and surgical wound infections. While in measles, raw surfaces do not exist on which infection can occur, this disease renders the respiratory mucous membrane especially vulnerable to infection with streptococci. Possibly in other diseases, as scarlet fever and even lobar pneumonia, similar conditions exist. When infection is once started in a ward in which the patients are closely associated, the streptococci become widely distributed; they probably gain in virulence with repeated transfer through the human subject, and serious and widespread infection results.

Probably the conditions in this hospital are not unique. It is possible that the widespread incidence of fatal pneumonia in the other army hospitals may have a similar explanation.

Part II.—Pathology[1]

By W. G. MacCallum, M.D.

The material for the following study was derived from thirty-seven necropsies performed on the bodies of patients who died in the base hospital of Fort Sam Houston, Texas. They were selected as cases of pneumonia, but in three of them it proved that death had resulted from other causes. Nevertheless, the lungs in these patients as well as those from several other miscellaneous cases in which the necropsies were performed by the resident staff, were studied.

The results are by no means easy to analyze, since there are many complications, many combinations of different infections, and many variations arising from differences in the stages of the disease at which the patient died. Briefly stated, however, it appears that

[1] This part of the work was carried out with the assistance of Lieut. W. C. von Glahn, M. R. C., U. S. Army.

two main types of bacterial infection are concerned. On the one hand, there are cases due to infection with one or another form of the pneumococcus; on the other hand, many cases have occurred in which a hemolytic streptococcus is the etiologic agent. Other bacteria have been found, notably the influenza bacillus, a gram-negative bacillus of undetermined nature, and occasionally one or another of the staphylococci; but all of these appear to be rather accidental invaders, and it seems scarcely probable that they are in any way responsible for the main anatomic changes.

Analysis of the cases appears to show fairly conclusively that the pneumococcus is responsible for those in which lobar pneumonia was found. The S. hemolyticus, in most instances, seems to cause a peculiar form of bronchopneumonia, which on account of its anatomic characters I have designated "interstitial bronchopneumonia." There are, however, some cases in which this organism, growing in overwhelming numbers or with especial virulence, produces a patchy pneumonia of a type more closely resembling the familiar lobular or bronchopneumonia found so often as a terminal event in persons dying of some chronic disease, or in those in whom aspiration of infected material has occurred. This may be referred to as "lobular pneumonia."

One of these infections may be superimposed on the other, and there may even be found lesions corresponding to each in the same lung.

Fibrinopurulent pleurisy with abundant exudate has occurred with extreme frequency in these cases.

Since it is recognized that pneumonia frequently follows measles, this relation was especially studied. There were fifteen definite cases of measles in the series, and in eleven of these the interstitial bronchopneumonia was found. Two showed, at necropsy, lobar pneumonia alone, two lobular pneumonia alone, while two presented a combination of lobar and interstitial bronchopneumonia. In all there were seventeen cases of interstitial bronchopneumonia, and in the six cases of this condition not definitely following measles no history of measles was obtained in five, although it was conceded that in the course of the great local epidemic these men might have passed through mild attacks of measles which were not mentioned

when the clinical history was taken. The sixth case was at first regarded as measles, but later as scarlet fever. From all the cases of interstitial bronchopneumonia the hemolytic streptococcus was isolated, and it seems clear that this is the true causative factor, whether it gains entrance on the basis of a predisposing measles or otherwise. Details concerning all these relations will be given in full in a later report, but in this preliminary report it is necessary to describe the following conditions as they occurred in this series: (1) interstitial bronchopneumonia; (2) lobular pneumonia; (3) lobar pneumonia; (4) empyema; (5) combined infections; (6) other complications.

1. Interstitial Bronchopneumonia. This is the condition already fairly well known through the work of Bartels, Delafield, Steinhaus, Hecht and others as occurring in children as a sequel of measles, whooping-cough, etc. Their descriptions correspond closely with what we have found in adults, except in the general lack of complicating empyema in children, and in certain minor histologic details, notably the presence in the lungs of children of extraordinary giant cells derived from the epithelium. None of these writers determined the nature of the bacteria concerned. On the other hand, although it has been recognized by various workers in this country that the hemolytic streptococcus is to be found in the bronchopneumonia following measles, none of them seems to have determined the exact nature of this peculiar bronchopneumonia. The association of the hemolytic streptococcus with the interstitial bronchopneumonia must, therefore, be especially emphasized.

The term "interstitial bronchopneumonia" was chosen as expressing briefly the salient features of the lesion. It may not be the most satisfactory term possible, because it fails to describe accurately the earliest stages, and leaves out of account the process of organization of the exudate which is very common; but any term that could describe the whole course of a progressive process would be unwieldy.

The interstitial bronchopneumonia has been studied in various stages in different cases and found to produce extraordinarily different appearances as it progresses.

In the earliest stage, the pleural surface of the lung is smooth and

glistening. The lung is, in general, air containing, although atelectatic patches may be making their appearance. On section, small hemorrhagic foci are found scattered through the lung, each showing, as a rule, a gray rather opaque center. These foci measure from 2 to 3 mm. in diameter, sometimes more, and are so small that several may occur in one of the secondary lobules of the lung, that is, in one of the lobules marked off by the interlobular septa (W. S. Miller). Microscopically, it is found that these foci represent the ends of the bronchioles together with the adjacent alveoli. The bronchiole and the ductulus alveolaris are filled with leukocytes, among which streptococci are found in pairs or in short chains. There is some infiltration of the bronchial wall with leukocytes, and the adjacent alveoli contain a few leukocytes, occasional streptococci, coagulable fluid, and great numbers of red blood corpuscles. Not only the alveoli which form a continuation of the bronchiole, but also those which lie near its wall, seem to be affected.

In a somewhat later stage the lung can still be distended with air, although the patches of collapse are more extensive. On section it is found to be studded throughout large areas with small, gray nodules which project above the cut surface like miliary tubercles, and are often surrounded by a red or grayish halo. At this time there may be visible a minute cavity or depression in the center of each which marks the lumen of the bronchiole. This may be represented, however, by the opaque contents of the bronchiole. These nodules have been mistaken by more than one for miliary tubercles, and it seems conceivable that the peculiar appearance of this and later stages may be in part, at least, responsible for the almost universal statement that measles is commonly followed by tuberculosis. Microscopically, such nodules are found to consist of a bronchiole filled with exudate of leukocytes, sometimes, but not often, associated with fibrin. The epithelial cell layer lining the bronchus is partly disintegrated or detached. The bronchial wall is hyperemic and thickened largely by the infiltration into its crevices of numbers of mononuclear wandering cells which have replaced the leukocytes. The alveoli about the bronchiole appear to contain less blood at this stage; only those immediately continuous with the ductulus alveolaris contain polymorphonuclear leukocytes; the others about the

bronchiole usually contain a network of fibrin with mononuclear cells. The alveolar walls in the immediate neighborhood of the bronchiole are thickened by an infiltration of mononuclear cells (lymphocytes, plasma cells and larger wandering cells). Surprisingly few streptococci are found, and those chiefly in the bronchial exudate. Fibrinopurulent pleurisy, often with excessive effusion of greenish, turbid fluid, accompanies the process from this stage on.

In a still later stage the lung is usually much collapsed, dark blue, flabby, and airless except in the anterior portions. This is produced chiefly by the pressure of the pleural exudate, but partly by the occlusion of the bronchioles. At this stage, shotlike nodules 3 or 4 mm. in diameter may be felt all through the lung. On section, the pasty, airless lung sinks into a concave surface, leaving the gray peribronchial nodules projecting conspicuously. The interlobular septa have by this time become greatly thickened and infiltrated with cells and fibrin so that they stand out most conspicuously as whitish-yellow lines, marking out the whole lobulation of the lung in polygonal fields. In each of these fields there may be three or four projecting nodules which now usually show distinctly a central bronchial lumen. The surrounding tissue may be fairly dense, so that the peribronchial thickening is marked out chiefly by its opaque whiteness. Hemorrhage may in some cases stain the outlying regions about the nodules. If the bronchi be opened with the scissors, they are found to be slightly dilated toward the periphery of the lung, where they become thick walled as they run into the terminal portion which forms the center of the nodule. The contents are thick and glutinous. Microscopically, such a lung shows a very great infiltration of the bronchial wall with masses of mononuclear cells. The epithelium usually still persists in places, although much of it is desquamated. The lumen is filled with exudate of leukocytes with rather few chains of streptococci. Sometimes all the lining of the bronchus has disappeared so that in cross-section it appears like an abscess. The walls of the adjacent alveoli are greatly widened and stuffed with mononuclear cells, desquamated epithelium, fluid and rather dense plugs of fibrin. Further out the alveolar walls are still thickened and infiltrated, and the alveoli contain chiefly fluid and desquamated epithelium. At this stage, organization of the exudate in the bronchi and the alveoli is usual. Indeed, this

organization occurs with surprising rapidity, so that it may be quite advanced in patients who have apparently been ill only about ten days or two weeks. In the bronchi the new connective tissue and bloodvessels arising from several points in the wall pervade the exudate and form richly vascular columns of fibrous tissue which extend into the alveoli and branch into each one. The lymphactics in the walls of the bronchi and bloodvessels and in the interlobular septa are distended with mononuclear cells and fibrin, and contain numerous bacteria. The bacteria apparently reach the pleural network in this way, and this seems to be the most plausible explanation of the infection of the pleura. The interlobular septa and perivascular tissues are densely infiltrated with wandering cells and become very conspicuous. The pleural surface is covered with a thick, shaggy layer of fibrin, and the pleura itself is greatly thickened by being converted into a vascular granulation tissue which is gradually replacing the fibrin.

Streptococci are present in great numbers on the surface of the fibrinous exudate, as well as in the purulent fluid in the cavity of the pleura. It is to be noted that they, unlike the pneumococcus, are not to be found scattered everywhere in the meshes of the fibrin. It seems possible that they may digest and destroy the fibrin, but at any rate they are found only on its free surface. They are not engulfed by phagocytes as freely as are the pneumococci, and they are found less frequently in the tissues themselves. Even when in an inflamed tissue, such as the lobulated, fat masses which project into the pleura from the outside of the pericardial sac, streptococci are found in a matted layer over the free surface, they can be traced down into the crevices between the lobes of fat only so far as these are freely open. If the surfaces adhere no bacteria are found in the obliterated depth of the crevice.

In still later stages, more extensive infiltration of the peribronchial tissue occurs, and solid yellowish patches from 1 to 2 cm. in diameter appear. The induration about these, with edema and hemorrhage, becomes confluent, so that quite large areas may appear consolidated. As to the nature of the healing process and recovery from this change, we have had no opportunity to learn anything.

In one case in which in some parts of the lung the lesions just

described occurred in a moderate stage of advancement other areas showed a great increase in the number of streptococci, with a wide dissemination into the tissue and a correspondingly intense inflammatory reaction. In other cases, much later, after a long course in which empyema of long standing has been drained by operation, the lung has been found to contain extensive abscesses, sometimes confluent into large, purulent areas. In such cases, and in these alone, one may expect to find secondary lesions in distant organs. It is rather remarkable that this particular hemolytic streptococcus seems to be an organism of rather slight virulence, with no tendency to spread through the body. Septicemia occurs only in the hours just before death, if at all, and in only one protracted case was there found an infarct-like lesion in the spleen. In all the others, the abdominal organs were normal.

2. Lobular Pneumonia. In these cases there was evidently an overwhelming infection with a virulent organism, or what amounts to the same thing; the patient offered no resistance to the invasion. The lungs present irregular, patchy, hemorrhagic areas of consolidation which are not especially peribronchial or limited in size. In them the streptococci are found in amazing numbers, often in long, tangled chains, scattered through the alveolar contents as well as in the exudate in the bronchi. In this respect the condition contrasts with that found in the interstitial bronchopneumonia. The exudate itself is chiefly composed of polymorphonuclear leukocytes, with some blood. There is nothing especially characteristic about this process, but it does occur after measles and is sometimes associated with the formation of areas of necrosis of the whole tissue which subsequently assume the appearance of abscesses. These are really not typical abscesses, but rather necrotic areas of consolidated lung tissue loaded with great numbers of bacteria. There were four of these cases.

3. Lobar Pneumonia. Thirteen cases of lobar pneumonia occurred in this series and presented the well-known anatomic picture which need not be described. In ten of them the pneumococcus was found, but in the remaining three it was missed, apparently because it was overgrown by the hemolytic streptococcus or by other organisms, since all of these were protracted cases with empyema, in which

death occurred some days after operation and drainage of the open pleural cavity.

In four cases, pneumococcus Type IV was isolated. Two showed the presence of Type I and two Type II. In two the type remained undetermined.

It seems very probable that in all the cases the lobar form of pneumonia was caused by the pneumococcus. In those in which the pneumococcus was not obtained in culture, organisms morphologically like them and having the characteristic distribution of the pneumococcus are seen in the sections of the affected lung.

Secondary infection with the hemolytic streptococcus seems to have occurred in some cases, although it remains difficult to tell whether the streptococcus may not have preceded the pneumococcus. In two cases in which the pneumococcus seemed to predominate at necropsy, it was thought probable that the streptococcus infection had been followed by that with the pneumococcus. On the other hand, four or five cases showed the streptococcus in great numbers at necropsy, while the pneumococcus was found only in such lesions as a vegetation on the heart valve or an abscess in the rectus muscle. In one case the pneumococcus was found only in the pleural fluid. In another it had been present in the blood before death. In such cases it seemed probable that the pneumococcus had been outgrown and replaced by the streptococcus.

Of the thirteen cases, five showed the pneumococcus alone. In none of these was there any empyema or excessive outpouring of fluid pleural exudate. But of the remaining eight cases in which there was also a streptococcus infection, there was empyema in all except one, in which both pleural cavities were obliterated by old adhesions.

Certain histologic features with regard to the distribution of pneumococci may be mentioned. While in the case of the interstitial bronchopneumonia the streptococci are in most cases present in relatively small numbers and then confined chiefly to the exudate in the lumen of the bronchus and the immediately adjacent alveoli, to the contents of the lymphatic and the surface of the pleural exudate, the pneumococci in lobar pneumonia are present in great numbers and are scattered diffusely through the whole lung and

everywhere through the pleural exudate. It is true that there are some cases of intense infection in which the streptococci grow in immense numbers throughout the affected portions of the lung; but ordinarily they are not to be found, or only rarely seen in the fibrinous exudate of the outlying alveoli. In the lobar pneumonia the pneumococci are rather more abundant in the bronchioles and ductuli alveolares than in the more peripheral alveoli; but many are to be found intimately mingled with the network of fibrin in all the alveoli and in the pleural exudate. The activity of phagocytes appears to be far greater in the case of the pneumococcus, so that great numbers of them are found enclosed in the leukocytes, while most of the streptococci appear to lie free in the exudate.

The transportation of the organisms by way of the lymphatic channels, in the walls of the bloodvessels, and interlobular septa and pleura is striking in the case of the pneumococci, as well as of the streptococci. It seems probable, although not proved, that it is in this way that the pleura becomes infected. Injections of the lymphatics from the pleural network gave beautiful preparations showing the connections of this network with the enormous, deep lymphatics which run toward the hilum of the lung, in the walls of the bronchi and bloodvessels, and in the septa. These aided in the recognition of the relation of the bacteria to the lymph channels.

4. Empyema. Empyema occurred in twenty-six of the thirty-seven cases of the series. In every case in which there was empyema, S. hemolyticus was demonstrated, and although empyema occurs in pure pneumococcus infections, only those cases in this series in which there was also a streptococcus infection developed actual empyema. The exudate appears quite early in the cases of interstitial bronchopneumonia, and is usually a thin, turbid, greenish fluid with floating shreds of fibrin and a relatively thin, fibrinous covering over the lung. Usually this fibrinous exudate cannot be readily peeled off, but is intimately adherent to the lung and partly organized. Very large amounts of fluid may accumulate—in one instance several liters. The effect is, of course, largely mechanical, causing the collapse of the lung, with corresponding cessation of its function; but it seems that the presence of such a huge culture of streptococci, which appear to grow in enormous numbers in a posi-

tion in which they are removed from actual contact with the tissues, must be a serious menace to the patient. Further studies should be made with regard to the toxic properties of this fluid and to the presence of bactericidal substances there.

After operation, the pleural cavity tends to become infected with various organisms which confer an extremely foul odor on the exudate. Encapsulated pockets of purulent fluid are often found between the lobes, even though the main cavity may have been fairly well emptied.

5. Combined Infections. Mention has already been made of the fact that both the pneumococcus and the streptococcus may occur in the same individual, and clinical study may show definitely which of these infections appeared first and which was superimposed. It is difficult to arrive at any conclusion as to this from the anatomic conditions, for the ordinary criteria of the duration of an inflammatory process—organization of exudate, production of mononuclear infiltration and indurative new growth of tissue in the framework of the lung—appear so rapidly in the interstitial bronchopneumonia and are so delayed in lobar pneumonia that they help but little.

In three cases there has been found in the lungs a definite intermixture of the anatomic lesions of lobar pneumonia with those of interstitial bronchopneumonia. These conditions seem to tend to exclude each other to some degree, even when they occur side by side in the same lung; but in some places the characteristic lesions of interstitial bronchopneumonia are found embedded in the uniform consolidation of a lobar pneumonia, emerging clearly into view as one leaves the area of lobar consolidation and passes over into the rest of the lung. In two cases the pneumococcus was recovered from the area of lobar consolidation, the streptococcus from the uncomplicated foci of interstitial bronchopneumonia in the same lung. These organisms are, however, too much alike, morphologically, to allow one to recognize them with certainty, in stained sections, in association with their specific lesions, when they occur together.

6. Other Complications. Complications with regard to other organs are rare in the cases of infection with this hemolytic strepto-

coccus. Pericarditis occurred a few times, but most of the cases of pericarditis were associated with pneumococcus infection. Otitis media is recorded in several cases. There were two cases of acute nephritis, probably not dependent on this infection, since the kidneys in all other cases were normal. On the whole, there seems to be a very striking absence of involvement of any organs other than the lungs.

The range of complications in the case of pneumococcus infection has been rather greater. There were four cases of pericarditis, one of peritonitis, one of symmetrical bilateral abscess of the rectus abdominis muscles, and one in which death occurred suddenly in convalescence, from embolic occlusion of the pulmonary arteries.

Summary. In the Army camps represented in this hospital, measles has been prevalent. Pneumonia occurred frequently, but not always as a sequel to measles. The nature of measles is unknown, and we have had no opportunity to learn what anatomic changes measles alone can produce. But it does produce coryza, conjunctivitis and laryngitis, and these conditions appear to predispose to infection of the respiratory tract with bacteria. This predisposition is made evident by the great proportion of the cases of the series in which streptococcus infection followed measles; but it is evident that streptococcus infection may occur in a person who has not had measles, and it is quite probable that other diseases, such as scarlet fever, predispose to its entrance in the same way as measles. When S. hemolyticus gained a foothold, it usually caused in this series of cases the anatomic complex called here "interstitial bronchopneumonia." This is the same whether it is preceded by measles or scarlet fever, or by no other disease, and its characters are due to the specific effects of the streptococcus. When lobar pneumonia followed measles, the pneumococcus was in this series accompanied by the streptococcus, and in some cases the lobar pneumonia was complicated, anatomically, by the corresponding bronchopneumonia.

Infection with the hemolytic streptococcus does not always cause an interstitial bronchopneumonia, but may produce a patchy lobular pneumonia.

One of the most interesting features of our study of the cases in this hospital is the recognition of the invariable connection of S.

hemolyticus with that characteristic anatomic lesion which was well known, but to which we have for convenience given the name "interstitial bronchopneumonia." This lesion is easily recognized in all its stages by its gross appearance, since the prominent gray, solid peribronchial nodules with surrounding edema, hemorrhage, organization and induration bear no resemblance to areas of pneumonic consolidation, which are homogeneous, solid patches, on the cut surface of which a plug of exudate projects from each alveolus. The microscopic appearance, as described above, is equally specific and characteristic, and there is no possibility of confusion with lobar or lobular pneumonia.

Empyema is a practically constant accompaniment of this condition, and is of extremely serious import.

The organism does not seem to be very virulent, and there is little tendency for it to enter the blood stream or to produce complicating lesions in distant organs.

Lobar pneumonia due to the pneumococcus has been found in many cases, not especially related to the occurrence of measles, but often complicated by secondary or coincident infection with S. hemolyticus. Its characters are exactly as seen elsewhere.

DISCUSSION

Dr. Wadsworth said: Although I have not had a chance to study the section microscopically, it is my impression that the lesions which Dr. Cole and Dr. MacCallum describe in these cases of pneumonia developing in the Army camps and which have been attributed very largely to the streptococci occur also in animals under experimental conditions. In both rabbits and dogs I have made a series of studies of the lesions induced by the pneumococci, streptococci and staphylococci, chiefly with a view of studying the development of organizing pneumonia. Usually the pneumococcus disappears during the earliest stages of the exudative process which it induces in the lungs of rabbits and dogs. Frequently, and especially in the rabbit, the bronchial type of lesion is found with infiltration of the alveoli walls extending out from the bronchus into the lungs with varying degrees of exudate into the air-passages in conjunction with the infiltration of the lymphatic tissues, which extend along the bronchus, but these lesions

invariably resolve and in them practically no organization was seen when the agent was the pneumococcus. But when streptococci, and especially staphylococci, were introduced experimentally with the pneumococcus the character of the lesions differed materially in that there was more necrosis and considerable organization to be found in the lesion. Furthermore, streptococci and staphylococci persisted a much longer time.

I also examined the lungs of three fatal cases of organizing pneumonia in man, which I obtained from the Museum of the College of Physicians and Surgeons. In these lesions, despite the fact that they had been preserved for a long time, it was possible to demonstrate the presence, morphologically, of large numbers of streptococci, some of them in long chains situated in the lesions, suggesting that they were the inciting agent, although it is, of course, difficult to exclude the possibility of the antemortem invasion developing as an infection secondary to the organizing pneumonia.

STUDIES ON SOME UNUSUAL TYPES OF DIARRHEA

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In presenting very briefly a few groups of cases of diarrhea of unusual etiology of interesting therapy, and by diarrhea we mean an increase in frequency and a diminution in consistency of the stools, we must realize that the mechanism controlling peristalsis lends itself peculiarly to such deviations from the normal. Although normal peristalsis is in a large sense automatic and under the control of Auerbach's plexus, we know that both intrinsic and extrinsic stimuli may profoundly disturb this mechanism. An increase of the normal stimuli—chemical, mechanical, thermic; the presence of pathological stimuli within the intestinal canal; variations in gastric, pancreatic and intestinal secretions, with their possible influence upon the elaboration of a peristaltic or antiperistaltic hormone, the presence of abnormal or the increase of certain normal constituents in the circulating blood; vasomotor disturbances probably of splanchnic origin, disturbances of innervation, either vagal stimulation or splanchnic inhibition, abnormality of nerves or ganglia, emotional disturbances—psychogenic factors; local stimuli due to the products of inflammation or to variations in the bacterial flora, all of these may lead to such disturbances in the motor sphere of the intestine as to produce diarrhea.

We shall, of course, not call attention to any of the more usual forms, such as that associated with enterocolitis, uremia, chronic passive congestion, myocardial disease, amebic, bacillary or other definite intestinal infections, or that met with during the course of many of the acute or chronic infectious diseases, but shall confine our attention to cases of unusual etiology which we have had the

opportunity of studying intensively. We shall present in order the diarrhea of achylia gastrica, the so-called gastrogenous diarrhea, that representing the first sign of hyperthyroidism, that following certain cases of cholecystectomy, diarrhea in tabes, diarrhea in sprue, diarrhea in certain cases of acute and chronic appendicitis and that associated with diffuse ulcerative proctitis, sigmoiditis and colitis.

Gastrogenous Diarrhea. This is a most interesting group comprising a very large number in our series, associated with an achylia gastrica, absence of hydrochloric acid, and usually marked diminution or absence of pepsin in the gastric contents, one subgroup definitely following shock or nervous strain, the other representing the terminal stage of a true gastritis, often senile, often associated with deficient or defective or diseased teeth. A very careful quantitative estimation made by us of the trypsin and diastase in the stool shows that these cases are not as Gross has suggested —pancreatogenous—for in all our cases analyzed the pancreatic secretions were normal. We do not believe with Nothnagel that this simply represents an enterocolitis due to the irritation of the intestine by the connective tissue, cellulose, etc., not properly digested or chymified in the stomach, but that there is another mechanism at work. Why should there be many achylias with constipation? Why should such very small doses of hydrochloric acid, far too little to help digestion or materially inhibit bacterial growth, cure almost immediately the majority of these cases? We have therefore felt that the hydrochloric acid probably plays a definite role in the elaboration of a peristaltic or antiperistaltic hormone, and that these cases, etiologically speaking, are partly due to an increase of the normal peristaltic stimuli, partly hematogenous.

Diarrhea in Graves's Disease. As a symptom of well-established exophthalmic goitre, diarrhea is, of course, a common phenomenon. We wish to report, however, a small group of cases in which, for a considerable period of time, in two of the cases, more than a year, the diarrhea represented the only symptom of the disease, although subsequently the clinical symptoms appeared. In all these cases there was a gastric achylia, but this is obviously

of no special moment, as practically all cases of the opposite condition—myxedema—also show achylia, and yet in these cases constipation is the rule; also hydrochloric acid therapy alone is, as a rule, ineffective in these cases. Therefore, there is probably a large element of thyreogenous disturbance of nerve impulses in these cases as the prime cause, very similar to those seen, for instance, in the usual tachycardia of these cases, though whether this is vagal stimulation or splanchnic inhibition one cannot say. There is also possibly some functional pancreatic disturbance, though in our series this seemed to have played but a small role, as the most thorough examination of the stool showed no disturbance in fat digestion. These cases are interesting in drawing attention to the fact that for a long period of time intractable diarrhea may be the only symptom of Graves's disease, and unquestionably a considerable proportion of the cases of so-called nervous diarrhea fall in this category, although some few possibly may be due to disturbance of adrenal function.

Diarrhea after Cholecystectomy. We have been much interested by the fact that in a small—a very small—proportion of cases after cholecystectomy the operation of election of many surgeons in gall-bladder disease, there develops a most intractable diarrhea. The gastric juice is usually normal. The examination of the pancreas at the time of operation shows that it is healthy. Very careful quantitative ferment studies of the stools in two of these cases showed almost complete absence of diastase and trypsin, suggesting that these cases must be regarded as pancreatogenous in origin, due to a reflex functional inhibition of pancreatic secretion, and this view is supported by the fact that relief is almost instantaneous with the administration of pancreatin and lime salts by mouth, a most interesting example of glandular therapy.

Diarrhea in Tabes. We have had a few cases of tabes dorsalis in which instead of the rather typical gastric or colonic crises the gastro-intestinal picture has been one of periodical attacks of severe diarrhea, although both gastric contents and stool are usually practically normal. These cases are probably truly neurogenic and represent either overstimulation of vagi or inhibition of splanchnics.

Diarrhea in Sprue. Three cases of sprue—a disease of peculiar interest to us on account of its prevalence in certain of our tropical or subtropical possessions, and probably due to infection with one (M. psilosis) or perhaps several of the varieties of Monilium—have been studied by us. Our stool studies showed a complete absence of trypsin and diastase: thus an absolutely different picture from that met with in pellagra in which our stool studies showed no pancreatic deficiency. In the treatment of our small series brilliant results were obtained by administering large doses of pancreatin in addition to the usual dietetic treatment. Whether this is an organic or functional disturbance of the pancreas and whether it is associated with atrophy of the intestinal mucous membrane I do not believe we can say, though the first seems more probable. We have not had the opportunity of trying a vaccine made from the monilium in the treatment of sprue, although we have heard that certain cases have been successfully treated by this vaccine in the army, which is incidentally rather contrary to the experience of the English. In one of our cases still under observation, and clinically absolutely well under treatment, we can reproduce the symptoms of the disease by stopping the administration of pancreatin for a short period of time.

Diarrhea in Appendicitis. A most interesting, instructive and comparatively large group is that met with in appendicitis, in which instead of the paretic gut with intractable constipation as one of the cardinal symptoms we have diarrhea. In our experience this occurs in two types of cases: (1) in the acute cases, especially in children, in which operation demonstrates that the appendix is very long and is situated in the pelvis, often close to or in direct contact with the rectum, thus calling attention to the value of rectal examination in these cases, and (2) in the other, chronic or subacute appendicitis in adults in which also, as a rule, a very long appendix is found, usually filled with concretions, rarely associated with extensive adhesions, and often again situated in the pelvis; in both of these cases appendectomy is almost always followed immediately by disappearance of the diarrhea.

Diarrhea in Ulcerative Colitis, Sigmoiditis and Proctitis. There is no more interesting group of cases of diarrhea than that

with which the name of Albu is associated, cases of most persistent and intractable diarrhea in which all the usual treatments, local as well as general, prove unavailing, and in which, on careful sigmoidoscopic examination, one finds many small superficial ulcerations of the mucous membrane of the rectum and sigmoid and presumably also of the colon. We have met with a number of these cases—among the most difficult to treat of any in our series. The gastric juice is usually normal; the stool, except for the presence of traces of occult blood and a few pus cells, is, as a rule, also normal, and in the few cases in which we have tried it the most careful bacterial examinations, both under aërobic and anaërobic conditions, has failed to demonstrate any specific bacterium as a causal factor. Notwithstanding this, however, we feel that these cases are probably not trophic, due to nutritional disturbances nor to perversion of intestinal secretion, but are probably due to some bacterium or protozoön, probably one only capable of growth under anaërobic conditions, because in all of these cases in our experience temporary cure follows rapidly after appendicostomy or cecostomy; in other words, after the lower bowel can no longer be considered anaërobic as a culture medium. Unless, however, the appendicostomy be kept open and irrigations continued through it for a long time—we have rarely allowed it to close under three months—this type of diarrhea is peculiarly liable to recur with a reappearance of all of its clinical features.

These, then, are briefly the groups of cases of unusual types of diarrhea which we wish to present:

1. The gastrogenous diarrheas met with in true achylia gastrica, probably representing a disturbance in the formation of peristaltic or antiperistaltic hormones, as well as an enterocolitis due to improperly chymified foods, and, as a rule, cured almost immediately with small doses of hydrochloric acid.

2. Diarrhea as an early and often almost the only symptom of exophthalmic goitre—probably fundamentally a diarrhea of neurogenic origin.

3. The diarrheas met with in a small percentage of cases after cholecystectomy, probably definitely due to a functional diminution of pancreatic secretion.

4. The diarrhea of sprue, which, while probably due to the monilium infection, has, as a powerful secondary factor, profound changes in the pancreas, as shown by complete absence of pancreatic ferments in the stool, and, as in the preceding group, much helped therapeutically by the administration by mouth of pancreatic extract.

5. The diarrhea in tabes, probably due to disturbance of innervation (possibly psychogenic), a motor equivalent, as it were, of the gastric or colonic crises met with in this disease.

6. The diarrhea in certain cases of acute, subacute and chronic appendicitis usually associated with a pelvic appendix, in which appendectomy almost always brings immediate relief.

7. The diarrhea associated with minute erosions of the mucous membrane of the large intestine, probably due to infection with an anaërobic bacteria or protozoön, and relieved, temporarily at least, by appendicostomy and irrigation through the new opening, that is, by cleansing treatment plus the changing of the lower bowel from an anaërobic to an aërobic culture medium.

DIAGNOSIS PER EXCLUSIONEM IN ORDINE: GENERAL AND PSYCHIATRIC REMARKS

By E. E. SOUTHARD, M.D.
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Is there any excuse for a communication on the general theory of clinical diagnosis? Should not one in the present concrete state of medicine apologize for any generalization or theoretical handling of a topic which has long since passed into the realm of the dead? If medical schools rarely nowadays, and only as a *curiosum*, deal with the some time familiar disciplines of so-called medical propedeutics and the logic of medicine, is it not for the very good reason that medicine no longer requires any propedeutics or any special overhauling of its logic?

I have two possibly tenuous excuses for the attempted resurrection, namely, first, that it is a canon of mental hygiene to get in imagination as far away as possible from our terrible environment; and secondly, that the realm of dead notions somewhat well befits a pathologist who has gone into psychiatry.

Speaking to a group of eminent clinicians, I need not insist that I myself make no claims to being a diagnostician of the first water. But just as more or less valuable books on elocution are written by persons without color or pretence of oratory, so perhaps one who is not an especially good diagnostician may descant humbly on the matter. Some five years ago, when I became director of the newly founded Psychopathic Hospital in Boston, it became for the first time my duty to deal concretely with a large series of clinical diagnoses. To be sure, before that time, and in fact, in the year 1909, I had been charged with the task of supervising the clinical and pathological research work of the State institutions for the insane of Mas-

sachusetts, and had already at that time begun to agitate upon the manifest errors in diagnosis which appeared in a small but definite minority of cases of mental disease in these institutions, as tested by the stern criteria of the autopsy table. I took an especial interest in errors of diagnosis in that mental disease entity, about which we know the most, namely, general paresis,[1] and found that one of the most active and thoroughly educated State hospital staffs in the country, namely, that of the Danvers State Hospital,[2] was none the less able to make an error of anywhere from 5 to 15 per cent., according to the fineness of the criteria adopted in the disease general paresis. After all, this work and sundry other articles by my associates and myself[3 4 5 6] remained quite upon the theoretical or unapplied level.

Suddenly, in 1912, I was translated to a region in which exceedingly rapid, not to say provisional, or not to say "snap" diagnoses had to be rendered in what almost any one would concede was the most difficult field of clinical diagnosis, namely, the diagnosis of mental disease. When it is remembered that the task at the Psychopathic Hospital is largely the temporary care of acute, incipient, and curable cases together with a consideration of almost dubious cases in the community,[7] it will be seen that the problem of a reasonably accurate diagnosis in these cases is not at all easy. It is necessary to remember, also, that our task is not that of the alienist so much as that of the psychiatrist, employing these terms in the differential sense recently advocated in a paper on the nomenclature of mental hygiene.[8] It is not the task of the Psychopathic Hospital to determine, except in a minority of cases, the committability or survivability of its patients. Of the first 5000 discharges from the Psychopathic Hospital, over 1700 were discharged as "not insane," a term which signifies, not that the patients had recovered, but that they were regarded as not having been insane during their stay at the hospital (the recoveries are over and above the 1700 "not insane"). In short, the task here is one of securing a basis for treatment and counsel for cases that lie often entirely without the purview of governmental control as mechanized by the probate courts. A large part of our problem is medical in the strict sense and not medicolegal.

I may be pardoned for insisting upon this peculiar and almost unique feature of the Psychopathic Hospital work in Boston, because not even my colleagues in the specialty of mental diseases have readily grasped the point. *Alienists* are a type of physician specializing in medicolegal practice, and their task is to determine alienation; that is, the theoretical or practical committability of their cases in the interest of the public welfare. *Psychiatrists* are a type of physician specializing in mental diseases on a much broader basis, namely, the basis of finer diagnoses, involving groups of mental disease and defect, and the psychopathic trends which fall short of defined psychoses and even the quicksand topics of eccentricity, crankiness, and oddity. *Alienistics*—a medicolegal field—is pretty sharply distinguished from practical psychiatry,—a medical field. A good psychiatrist ought to be able to accommodate himself to governmental groups well enough to be a good alienist; but, on the other hand, many a good alienist who has dealt for years with the category of committability only, is unable quite to see the point of a diagnosis of "Psychotic, not insane," or of "Psychopathic, not insane." The question of nomenclature is subordinate; but aside from the question of nomenclature, if the practitioner cannot grasp the distinction between insanity in the medicolegal sense and mental disease in the medical sense, he is a man unable to keep pace with the modern progress in psychiatry.

What, we may ask, has the question of psychopathic hospital diagnosis of psychoses that fall short of insanity to do with the topic assigned for this communication? How does this work fit into a discussion of the general theory of clinical diagnosis? Psychiatrists have always taken a great deal of interest in classification. I will remind you only of the eminent instance of Pinel, who in 1809, published a *nosographia methodica*, which is one of the best-known of the old nosologies, a very good general view of which is given in Hosack's publication in 1819.[9] I am afraid, however, that most modern practitioners, and especially in America, would be apt to deride it as out of date, if not fundamentally beside the point of these adventures in classification. Of course, these scoffers have the entire interest of science against them in their scoffing. But the modern practical fellow, especially the pragmatic American, little

recks such a small matter as consistency with the general history of science. Nor will I attempt to defend the various excesses of nomenclature to which my psychiatric superiors, both in point of time and in point of capacity, have sometimes perpetrated. It is another queer way which Americans (and I suspect other moderns) have, namely, to confuse the topic of nomenclature with the topic of classification. Classifying for these persons means assigning a name. To be sure, a slight re-reading of that apostle of clarity, John Stuart Mill, would perhaps set these confused minds aright. Still I suppose it is too much to ask of them to re-read even a few chapters of Mill's *System of Logic*.

What, after all, constitutes diagnosis? I do not know whether the Harvard Medical School curriculum is less logical than those of other medical schools that the American Medical Association terms *Class A*, but it is very hard to get from a Harvard Medical School student at any stage, even immediately after securing his M.D., an adequate definition of the terms *diagnosis*, *symptom*, and the like. Yet would any one of us suppose that these terms can be safely dispensed with in practice or in theory? And even if you could somehow show that a pragmatic view of medicine might throw overboard altogether the distinction between disease entity and disease symptom, nevertheless the books are full of these terms used in a variety of ways, and I am sure it ought to be the duty of every medical course to offer some pabulum (whether propedeutic or by way of appendix) on these matters, which were doubtless comprised in the forgotten and discounted field of so-called Medical Logic.

Many a favorite text-book in the practice of medicine fails to make any point whatever of this distinction, and plumps one forthwith into a discussion—*e. g.*, of typhoid fever—jauntily assuming that the student somehow knows by intuition the meanings of the terms, *definition*, *entity*, *diagnosis*, *symptom*, *symptom-complex*, *syndrome*, and the like. Perhaps, however, it is better to leave out general remarks in this direction than to put in some which are found in certain other text-books that have run into many editions. Strümpell[10] makes no special point of the matter but insists in a preliminary note upon the importance of diagnosis, of clinical observation, and of keeping the common courses of all diseases in

mind. Here, perhaps, is the most commonplace remark nowadays about diagnosis: diagnosis, namely, is constituted by observation, according to these authors. In fact, there is one text-book (Wilson[11]) that summarily states upon its title-page that the whole art of medicine is in observation. On a later page it is insisted not quite so broadly, that "it is certainly true that the art of diagnosis is an art of observation;" and again, "The facts of pathology and semiology and the natural history of the diseases constitute the basis of diagnosis." This latter statement seems almost equivalent to the statement that the facts of disease are the basis of diagnosis, which may be in one sense true, but is so little helpful that it might well be left unsaid. Another recent author (Hall[12]) states that "the art of diagnosis consists, then, in gathering all accessible data and arriving at that conclusion which seems the most reasonable as the probable cause of the trouble." This definition evidently goes beyond the former, namely, "Diagnosis is constituted by observation," by considering that the reason is necessary over and above observation. Put in these terms, of course no one of us would care to say that diagnosis consists in gathering data. Put baldly, it is certainly untrue to say that the collecting of facts constitutes the art of distinguishing among these facts. Yet the whole trend of recent work runs in the direction of insisting upon observation at the expense of reason. And, whether or not we teachers are entirely clear in our own minds as to the distinction between diagnosis and the mere recognition of fact as such, certainly our students are not always clear. A student will give the "diagnosis" *fever* or *rose spot*, when he would scoff at making the "diagnosis," *It is raining*, or *The engine is skipping*. If this be diagnosis, make the most of it! Of course, diagnosis is clearly a form of recognition, a form of knowledge, but there seems to be no warrant in raising every elementary form of awareness, kenning, or recognition to the level of diagnosis, which term bears within itself a manifest prefix, suggesting distinction, differentiation, sundering. All my own medical teachers, and I do not doubt the majority of those of my listeners, insisted upon the value of accurate observation. Few of them insisted upon the importance of correct reasoning. Most of them, I take it, partly as a matter of self-defense as they were growing older, were

quite sure that maturity of judgment was a thing not readily attained. It never seemed to occur to these teachers that, as the powers of observation were on the wane, the powers of right judgment were to increase. In brief, these teachers, without ever once using the term *logic*, and hardly ever the term *reason*, managed to get into their homilies for students the idea that there was something besides observation, namely, what they called common sense or knowledge of fundamentals, or keeping essential cases in mind, or ripeness of clinical experience, and the like.

Though I believe some course in propedeutics might well be constructed to contain the main principles of the logic of medicine, yet that is not the point of the present argument. Basing my notion upon the practical experience of the last few years, in which I have had contact with clinical diagnosis, always with the autopsy criterion more or less consciously in mind, I want to argue for a more extensive application of the principle of logic in practical diagnosis, and especially the practical diagnosis of the tyro. Perhaps you will think my argument is nothing more or less than a rehabilitation of the diagnosis by exclusion of the older authors. To some extent, the argument does follow that line, though the arguments have been derived from recent practical experience in off-hand and professional diagnosis, and from certain logical considerations. That older argument is found very well expressed in DaCosta's book so long ago as 1864.[13] DaCosta's book, according to an enthusiastic Philadelphian (Wilson[11]) marked an epoch in the progress of internal medicine; and surely many of DaCosta's distinctions are found in several text-books built upon the lines of his book for many decades after 1864. DaCosta distinguished direct and indirect diagnosis. Indirect diagnosis by exclusion, according to DaCosta, "is not on ordinary occasions much employed *nor indeed is it to be recommended*" (italics mine). It is this dictum of DaCosta which I would think ought to be combated in any summing up of present-day processes in diagnosis.

The reasons why DaCosta felt that diagnosis by exclusion was not to be recommended were assigned by him as follows: First, "to prove what a thing is by proving all that it is not, is a very tedious process." Secondly, DaCosta went on to say, "It is difficult

to think of all the possibilities." And thirdly, he said, "Pathology is in an imperfect state." Now, as for the latter two reasons, it is clear that the process of direct diagnosis is equally subject to the pitfalls of imperfect pathology, and equally subject to the charge that it is hard to think of all the possibilities. I myself can only believe that these two latter so-called drawbacks are not drawbacks worse for diagnosis by exclusion than for any other form of diagnosis. Accordingly, I believe that DaCosta's objection to diagnosis by exclusion reduces to its tediousness; but should we hesitate to say to our students that it is better to be tedious than wrong? The technic of DaCosta's process may be stated in his own words:

"To cite a case in illustration: A person consults us for a cough brought on by exposure. He has been sick for four or five days, having been previously in good health. We notice, on examining him, that his breathing is hurried, and that he has fever; the lower portion of one side of the chest is dull on percussion, and the respiration there is wanting; the action and sounds of the heart are normal. The facts point to the lung or its covering as the seat of the disorder. We know, furthermore, from the history and the febrile symptoms, that we have to deal with an acute affection. What are the acute pulmonary affections? Acute bronchitis; acute phthisis; acute pleurisy; acute pneumonia. In all there is fever, cough, and impaired breathing. Is it acute pneumonia? No; for, notwithstanding there is in this complaint, in addition to the general symptoms mentioned, dulness on percussion, such as we have here, the dulness is associated with a blowing respiration; whereas in the case before us no respiration is heard. Let us look at the sputum, and see if it is tenacious and rusty colored. It is not; it is thin and frothy. Moreover, the breathing, although hurried, is, when counted, found to be less hurried than it is in inflammation of the lungs. But acute pleurisy may explain all the signs. The patient, too, when questioned, states that he had at the onset a sharp pain in his side; and this we are aware takes place in pleurisy. The vocal vibrations, likewise, are noticed to be absent on one side of the chest, which, when carefully measured, is evidently enlarged. This corresponds in all points with what happens in pleurisy in the stage of effusion. The disease *is*, therefore, acute pleurisy in the stage of effusion. We finish the diagnosis by ascertaining the existence or non-existence of other maladies, and by taking note of the severity of the complaint; that it has occurred in a young and robust person of good habits; and that the symptomatic fever is very active."

But what is a direct diagnosis—one not made by exclusion? According to Wilson, "A direct diagnosis is made when the history

of the case and the clinical phenomena are sufficient to warrant a positive conclusion." Wilson goes on to say that a diagnosis by exclusion differs from differential diagnosis only in scope. Strange as this phrase may sound, it strikes me that there is a great deal of truth concealed in it. I feel that, so far from admitting with DaCosta, that diagnosis by exclusion is not much employed or to be recommended, practically every diagnosis is by exclusion, whether consciously or unconsciously.

Musser remarks concerning diagnosis that "the data collected are sufficient to warrant a positive conclusion. The direct method is scientific, rational and most practical. It is a practice of purely inductive reasoning." I am not sure whether it would not be sounder to say that it is a process of purely *deductive* reasoning, but modern logicians have conclusively enough proved that practically all reasoning is both inductive and deductive, so that it would not pay to quibble over the claim that direct diagnosis is "a process of purely inductive reasoning." As to the method of diagnosis by exclusion, Musser remarks, "Thus, a symptom group may suggest several diseases; each affection must be passed in review and excluded until one is found which closely corresponds to the data of the case under consideration." In short, it would seem that diagnosis by exclusion is an effect of the *force majeure* of complex and obscure data. The battle is easily won when it is a question of perceiving a symptom and suspecting a disease, whereupon all "the data collected are sufficient to warrant a positive conclusion."

Now, possibly it is the complex and obscure nature of mental disease which has caused me to feel that diagnosis by exclusion is a method that requires rehabilitation in the minds of teachers and in the pages of text-books. In medicine and biology at large in the middle of the nineteenth century, it was the fashion to denounce speculation and extol observation. So many of the medical and biological sciences depended upon the microscope and the visual process, that nothing was more natural than to see great virtue in observation as compared with the vagaries of the *Naturphilosophie*.[15] We are now so far beyond the range of that old *Naturphilosophie* (unless the idea of Pan-Germanism may be regarded as a remote

result thereof), that it should be quite safe to uphold the reason as entitled to a seat beside observation in the process of diagnosis. Applied logic accords to observation its full worth. Secondly, a proper value is assigned to what may be inaccurately summed up in the phrase *comparative method*. It is the comparative method probably that is being used in diagnosis for the most part at the present day. That is, one picks a symptom, suspects a disease, constructs a supposititious diagnosis, and proceeds to compare it with all the data of memory or reference books. It is all one, whether you pick one symptom—*e. g.*, the so-called presenting symptom[15] popularized by Richard Cabot—or assemble a symptom group; the process remains the same, that of matching the data of the case with some supposititious diagnosis. Now in the field of mental disease probably every one of you has had the experience of matching virtually all the symptoms of a case with the majority of those given in the text-books for several different mental diseases. In short, the comparative or matching process has been only too successful, and the diagnosis might well be rendered by lot from among a not very small group of text-book headings.

Of course, the comparative method involves the use of observation also. The distinction between observational recognition of a condition and the comparative determination of a disease by a direct method is not a mutually exclusive distinction. So also in respect to the third method of applied logic, namely, the statistical method. The statistical method requires both observation and comparison, but entails also certain new features. Probably Richard Cabot has popularized the statistical method of diagnosis more than any other recent author. Cabot finds a presenting symptom which becomes to him a lead. This presenting symptom is often something complained of by the patient, but also is often something noted by the physician that the patient did not subjectively recognize. Cabot has founded a differential diagnosis upon a selection of the most common presenting symptoms. He goes on to list the causes of these symptoms by their frequency, and then, to use his picturesque phrase, "follows the symptom home." Following the symptom home means, naturally, employing all manner of comparative and observational methods in addition to the merely statistical

one. Nor do I wish to give the impression that Cabot overemphasizes the statistical method in his account. He merely emphasizes it more than most previous authors. Nor would his account fail to insist that observation is indispensable, for he carefully states that diagnoses are missed usually because physical signs are not recognized. That is, for Cabot, poor diagnosis is usually a matter of poor observation. But occasionally diagnoses are poor on account of poor reasoning, and Cabot's book is an argument for a more comprehensive grasp of the possibilities of diagnosis. Others may insist upon the recognition of the symptoms and signs by proper methods of observation, and Cabot, like many others, has in other works given an account of these matters along approved lines; but he dreams for the purpose of differential diagnosis of a "cash-register of causes." He wants possibilities sifted. He wants clues, radiations and leadings followed out along lines that are essentially statistical. One proceeds from the presenting symptom to the possible causes; from the possible causes to the probable causes, and from the probable causes to the actual cause. In the technic of this determination, Cabot, as is well known, much insists upon the statistical configuration of the different conditions in which the various presenting symptoms are found.

Cabot notes that physicians in the matter of differential diagnosis "are very suspicious of any attempt to tabulate their methods of reasoning." He speaks of profiting much by Herbert French's *Index of Diagnosis*[16] (first published in 1912), a book which I find is greatly affected by medical students of my own acquaintance. French claims his index to be an index of main symptoms, though there seems to be no internal evidence in the book just how these main symptoms were selected. French, like Cabot, deals largely though not exclusively with symptoms complained of.

It is readily seen that Cabot's ideas (though they would have been readily comprehended by DaCosta in 1864, since they are founded upon the statistical principle which had already been a few decades in vogue in DaCosta's time) would not have appealed especially to him as important in the process of direct diagnosis. Feeling as DaCosta did concerning diagnosis by exclusion as a *dernier ressort*, he would not have seen the compelling value of Cabot's statistical

frequency tables for the distribution of symptoms in different conditions. Moreover, it is doubtful whether in 1864 hospital records were so extensively kept as nowadays, despite the fact that intensive records of special cases may have been kept at a relatively higher standard than now prevails in institutions where the real work is done more by interns than by visiting physicians.

The situation, then, is that in some cases what might be called an observational diagnosis can be rendered. Personally, I should feel that the term *diagnosis* was being prostituted somewhat when the diseased condition is recognized forthwith on the basis of some pathognomonic symptom or combination of symptoms. But let the phrase pass; the result of naming the disease and getting a practical basis for treatment is attained by a process of pure observation. The so-called direct method of diagnosis is hardly on a higher plane logically speaking than that of observation in many cases; but in others, and perhaps in the majority of cases, this process of differential diagnosis by the so-called direct method is one of comparison; that is, of matching the phenomena of the disease observed with those of some classical or text-book type. The unduly maligned method of indirect diagnosis, or diagnosis by exclusion, likewise employs comparison inasmuch as it excludes disease after disease by discovering that not enough exists to match the types in question. Having risen, accordingly, from a process of direct recognition (*gnosis* rather than *diagnosis* in any logical sense) to a process of somewhat less direct differential diagnosis by a positive matching or a negative excluding process, we finally arrive at a more modern technic of studying the frequency of symptoms in certain large groups of comparatively well-observed cases (the majority of Cabot's tables deal with 250 cases analyzed at the Massachusetts General Hospital). We notice that the process of observation is indispensable throughout. Extreme exactitude of observation is not perhaps so necessary in statistics as in individual cases; at least errors of observation may be assumed to balance themselves to some degree.

Is there no further sharpening of our technic of diagnosis? In the practical handling of the diagnostic problem at the Psychopathic Hospital, in the course of two years' observation I became interested in the fact that, where diagnoses were not matters of

mere observation and direct differentiation, but where processes of exclusion were necessary, I found myself endeavoring to exclude conditions in a certain *definite order*. It is this ordinal principle which I believe might constitute an advance in practical diagnosis, were it to be insisted upon in still other branches of medicine than psychiatry. I have recently made some endeavor to apply the principle to the situation in clinical neurology but shall not here mention the results of that inquiry in any detail. After the first two years of off-hand and provisional diagnoses at the Psychopathic Hospital, I then considered the matter of exclusion in a definite order for some three years before laying down the order in question (see below). I think it would be presumptuous for anyone in any special branch of medicine to draw up a definite order of diagnoses in any other. For example, however convinced I might be that diagnoses in dermatology are actually made consciously or unconsciously by some process of successive exclusion of conditions in a definite order, I should not (as I am far from being a dermatologist) have the slightest ground for suggesting an order for dermatological diagnoses, or a list of conditions to be put in order. Not being an internist in the field of cardiac disease (that is to say, not being in any sense an expert with the electrocardiograph and all the rest), I certainly could not advocate any particular order of diagnosis for heart disease, however strongly I might be convinced that such an order must exist.

At this point I looked into certain works of logic to learn what might be said concerning these different principles of diagnosis, and found in the late Josiah Royce's contribution entitled "The Principle of Order" in the *Encyclopedia on Philosophical Sciences*, an exposition very much to the point.[17]

I presume that most of us have few memories of logic except the syllogistic logic of such college text-books as that of Jevons. Some of the older among us will still have used Mill's *System of Logic*, or text-books closely modeled thereupon. The more recent advances in applied logic are a closed book to most college and medical students, but in addition to so-called formal logic used as an irregular discipline in most colleges, there is an applied logic or methodology which deals with norms of thought as applied to the methods of the

special sciences. The formal logic of a book like that of Jevons is only a very subordinate part of logic as at present defined. Royce speaks of the new doctrine as the science of order. This science, he says, is today in a very progressive condition, is in some notable respects new, and offers inexhaustible opportunities for future progress. Already in the Socratic and Platonic handling of these topics, the systematic nature of the world's construction, the objectivity of the world permitting inference concerning its various truths and the order that rational processes show, had already become clear. Types, forms and relations are at least as real as the facts of the physical world. Aristotle, Bacon, and still more importantly, Galileo, made important advances in logic. Today no one will question that every science in dealing with its facts must employ methods of classification in no wise different from the method used by Socrates in his dialects. To be sure, a science which uses only methods of classification must now be regarded as a very young science. Botany and zoölogy have long since passed the phase in which classification is the dominant interest. Anthropology, on the other hand, is largely classifying still, though there is some tendency to the development of a higher method of logic, the comparative study of the forms and results of human culture.

Royce mentions that, among the medical sciences, psychiatry is just now emerging from a stage in which the bulk of the science was made up of the classification of cases, symptoms and disorder. Psychiatry is now about to work on a higher plane of methods. The more complex the facts, the harder it is for a science to get beyond this first stage of classification.

What are these higher processes of applied logic? There are mainly two: The method of comparison and the statistical method. The comparative method compares the corresponding stages in the various processes of products of natural evolution in the science in question; whereas the statistical method uses exact enumerations as the basis of its science. Of course, the two methods are not always sharply to be distinguished; whenever one has to compare numerous evolutionary processes, all the results of these processes have to be enumerated. In these instances, however, the statistical method is merely an auxiliary to the comparative method. When, however,

we come to such matters as the mortality tables of insurance, the sociology of marriage and divorce, of suicide and crime, or of commerce and industry, we are dealing with topics in which the statistical method is virtually the only one at present available. We study, for instance, how human mortality varies with age; how the science of an organ or an organism follows conditions determined by heredity or environment. As a result of such statistical processes, the statistician becomes able to deal with aggregations or blocks of facts; orders or aggregations which may be treated as units of a higher order.

When sciences become developed still further, these two methods of comparison and statistics are used in a still more intimate manner, combined in a method which Royce terms the *organized combination of theory and experience.* By means of the statistical and comparative method, we discover laws of nature that have a certain degree of probability, the degrees of which we may trust on the basis of fair samples of the phenomena of the given science. We then construct laws on the basis of hypotheses derived directly from fair samples of fact. Hypotheses thus drawn may be of the simple type directly refutable or directly verifiable by immediate recourse to the facts; or on the other hand, hypotheses may require much more work for their testing. In fact, the more direct the proof, the more valuable the hypothesis, since the success of the hypothesis would here depend upon the falling in line of vast numbers of facts which on no other basis could be supposed to fall in line. To combine hypothesis, theory and observation, we first draw up a hypothesis regarding the constitution or laws of some region of physical fact. Upon the basis of this hypothesis, we make an extensive and exact deductive theory as to what *ought* to be present if the hypothesis is true. "The more extensive, exact and systematic the theory thus made possible proves to be, the larger are the possible samples of the consequences of the hypothesis which are available." We then collect samples of facts by means of observation and experiment, and proceed to compare them with results of our elaborate deductive theory. The more elaborate and extensive our theory, the larger the range of facts that we can draw upon for comparison. We are not now restricted to noting what proportion of members

of a sample have certain characters. On the other hand, if the deductive theory is a highly developed and elaborate one, we shall find that almost any sample available for comparison is minutely verifiable in detail with some part of the original hypothesis. In short, the value of this method depends upon "the exactness, the order and the systematic character of the concepts in terms of which the hypotheses thus directly tested are defined." It would thus appear from this highly condensed statement of Royce's view, that "the organized union of theory with observation requires for its perfection concepts and systems of concepts which permit of precise and extended deductive reasonings." It is surprising how small the samples need to be when it comes to a judgment as to the applicability of a highly complex hypothesis. A few small samples taken from widely separated parts of the system will prove or disprove the virtues of the hypothesis.

Without asserting that medicine is yet in a stage to profit like physics and chemistry from this organized combination of hypothesis, theory and observation, it is clear that many parts of medicine are far beyond the application of mere statistics or of mere comparison, and still farther beyond the modest virtues of pure observation.

Without venturing further at this time into methodology and modern applied logic, it is clear that mere observation, mere comparison of stages, mere enumeration, are not the whole story in any science. If the medical sciences are going to advance in their logic, it is more than likely that their logical advance will take place in the direction of a greater insistence upon order. I hold accordingly that, if Royce's exposition of certain modern developments in logic is a sound one, the next stage of development in medical thinking will be a reduction of its interests more and more to order and system. There is reason to hope that by the reduction of medical as well as any other scientific facts to order systems, a greater and greater success in deduction will be attained. I conclude, therefore, that when I found our process of diagnosis at the Psychopathic Hospital employing more and more the concept of order, I was simply discovering a small fact bobbing in the big stream of logical advance.

In the light of present knowledge, how almost naïve and childish appears the old dictum that disease is life under altered conditions! Here were but two elements: life on the one hand, and change on the other. Each contains a host of undiscovered statements of fact. How slender a contribution appears the claim that diseases must be instances of either the augmentation, the diminution, or the mere modification without increase or decrease of structures or functions. To be sure, bacteriology shortly yielded a dyadic system of germ on the one hand and host on the other, which for the moment and for a decade or so allowed one to hope that the formula "Disease is life under altered conditions" might be simply rendered into, "Disease is the effect upon an organism of a germ." Then came the contentions of Metchnikoff concerning phagocytosis, and the more complex interrelations of the host with its contained germ.

Shortly, in the nineties arrived triadic conceptions of the interrelation of the organism, the foreign substance, and sundry intermediary bodies; and early in this century was unfolded the still more mysterious situation of anaphylaxis. In short, the problems of medicine are becoming more and more rich and complex, more and more verifiable by small samples of fact taken at widely diverse parts of the system.

The rapid complication of the research situation in medicine at large, as typified especially by the facts of immunology, has its reflection also in the slower moving departments of clinical diagnosis. We see in text-book after text-book insistence on diagnosis as a matter of observation (going back very far, for example, to Baglivi[18]). We then found, as in virtually all the medical text-books in the latter half of the nineteenth century, a new form of assurance: The diagnostician is not now satisfied with what he calls direct diagnosis.

The aim here is to enroll the case in some definite group of diseases recognized by pathology. The difference between perceiving that "this fruit is an orange" and scientific recognition of a diagnosis is merely a question of degree. It is not so easy to say that "this is a case of typhoid fever," as it is to say that this fruit is an orange, because of the more concealed and special nature of the points on which we rest our diagnosis of typhoid fever. The method is one

of comparison of certain perceived characters or features with certain signs already known to us as pertaining to certain disease groups. Whether the symptoms are simple, like a friction rub, or complex, like the chemical analysis of a secretion; whether the symptoms are present at the time of examination or are merely anamnestic, from the diagnostic point of view, they are speedily divided into pathognomonic symptoms on the one hand, and more general ones on the other. The tubercle bacillus or the Argyll-Robertson pupil might be mentioned as examples of pathognomonic symptoms in this broad sense; whereas fever and vomiting would be examples of symptoms which belong in a great number of disease groups. But whatever the kinds of symptoms we recognize, the process of diagnosis appears to be one of comparison of those symptoms that we perceive with such symptoms as we know to characterize a given group of diseases, and upon the discovery that the symptoms of the disease in hand correspond with the symptoms of the disease type which we know from the books or from experience. We draw a conclusion, then, on the basis of similarity of symptoms. We may draw this conclusion from a pathognomonic symptom, which beyond any question indicates the existence of a given disease; or if no pathognomonic symptoms are present, we may ground our diagnosis upon the harmony between the general symptoms in our patient and the symptoms that belong to some described disease; and of course we are throughout well aware how unsuccessful may be a diagnosis based largely on the similarity of general symptoms to those of the books. This method of diagnosis, which we may briefly term the "type-matching" method, is doubtless the one extolled by the older workers under the name direct diagnosis. It represents an advance upon purely observational diagnosis—that is, diagnosis by inspection—and is a form of diagnosis by comparison.

Diagnosis by exclusion or by differentiation is a method somewhat decried by older workers and now brought into great prominence by such work as that of Cabot and of Herbert French. Though there is nothing logically new in this work, there is a new emphasis in it. It is still, logically speaking, an application of the comparative method greatly bolstered, as Cabot handles it, by the statistical method.

The general nature of differential diagnosis is somewhat as follows: As it is impossible to consider all the phenomena in a given disease, we first select a group of diseases in which a certain sign is found. We look in the case under observation for some more or less outstanding symptom. This common symptom which we would use as the point of comparison among diseases is called by Bieganski the *index of differentiation*, or the difference indicator. Cabot has more recently termed one form of it the presenting symptom. This indicator or presenting symptom is chosen because we by experience know that it occurs in a large number of diseases. To be sure, it is much better not to take a too-general indicator. Thus, in the question of typhoid fever, it would not be so advantageous to begin with fever, perhaps, as to begin with diarrhea. The process of differentiation now begins: We compare the case under observation with those diseases which we have found to be somewhat similar thereto. We pass from one disease group to another. We constantly keep upon one side the observed case with all its symptoms, and on the other the total series of diseases which in a certain respect are similar to it, namely, in respect of the common trait, index of differentiation, or presenting symptom. We proceed to look for differences. The observed case may not belong in a group because it does not possess the symptom which is constant in that group; though the indicator is possessed by both diseases, a symptom constantly present in the compared type is absent in the observed case.

Or the observed case may not belong in the compared group because there is a symptom in the observed case which never occurs in the compared group.

Again, the observed case is not the disease with which we are comparing it because we know that in the compared disease a symptom constantly occurs which is the direct opposite of some symptom observed in the case in hand. Moreover, there may be an incongruence of symptoms of a quantitative or qualitative nature, a difference which does not proceed to the point of complete absence or perfect antagonism of symptoms.

Following is a table which embodies the process-types of clinical diagnosis now in vogue:

TABLE OF PROCESS TYPES OF DIAGNOSIS.

I. Inspection.
II. Expectation.
III. Induction.
IV. Comparison.
    (*a*) Similarity.
    (*b*) Similarity and difference.
    (*c*) Difference.
V. Ex juvantibus.
VI. Ex nocentibus.

I may say at the outset that it is the endeavor of this paper, granting each of the three subordinate methods under the head of Comparison to be a separate logical method of diagnosis, to add a ninth method. This ninth method I shall choose to call "*Diagnosis per Exclusionem in Ordine.*" *Diagnosis per exclusionem in ordine* is merely a method of employing logical comparison of Type IV (*c*) of the above table *in an orderly manner.*

But before attempting to speak of this newly described type of diagnosis, I must briefly describe the eight classical methods so that I may, if possible, demonstrate that the ninth or proposed new method has novelty. For the purposes of this discussion I have gone rapidly over a great many of the older text-books of medicine, studying largely the logical remarks by their authors in the prefaces and introductions thereto. I then examined many of the text-books in Medical Logic which were for some years the vogue in medical schools. From the study of text-books, largely in the latter half of the nineteenth century, and from the study of works on Medical Logic I have arranged and combined the methods of the above table. I have been especially aided by the modern work of Bieganski, a Polish work available to me in German translation from its second edition. This work may be referred to for a good summary of the older points of view, together with the fruits of some Polish polemic in which Bieganski had for some years been engaged. The older work of Oesterlen,[20] published in Tübingen in 1852 and translated into English[21] in the Sydenham Series in 1855, is almost barren for modern purposes (so much so that I found the leaves uncut both of the original and of the translation in the New

York Academy of Medicine!). Of still older literature, the Medical Logic of Sir Gilbert Blane,[22] illustrated by conclusions concerning yellow fever, is of great interest, though his classification of the elementary principles of life as generative, conservative, temperative, assimilative, formative, restorative, motive, sensitive, appetitive and sympathetic, is an example of categories which, however true and feasible they may be from various points of view, are of little diagnostic value. This older work often fails to distinguish the question of classification from the question of what is to be classified. Sir Gilbert Blane's work upon yellow fever, and especially upon scurvy, derived from his expert contact with marine diseases in the British West Indian campaigns, is of greater value than his excursions into logic. Blumenbach calls Sir Gilbert Blane the most learned and classical physician of the age, but despite this German appreciation, little has been done in Germany of an original nature on medical logic. Oesterlen appears to be in the general nature of a physician's reaction to the logic of John Stuart Mill. Apparently someone was impressed with the possible value of such work as Oesterlen's, and Francis Ogston was given a new chair in Aberdeen as Professor of Medical Logic and Jurisprudence. In a syllabus[23] of his highly interesting course of thirty-two lectures, he refers to his indebtedness to John Stuart Mill and to Oesterlen, traces the history of the topic from Aristotle to Bacon, thence to Blane and Oesterlen, and comments upon the absurd distrust of theory which he found prevailing in Britain. Ogston called the merest routine practitioner a bold speculator and imperfect observer of facts. He remarks that the limits of pure observation in medicine are soon reached and discusses in separate chapters the inductive or analytic method as opposed to the deductive or synthetic method, rightly holding that the latter is a much more important concern of medicine than the former. Under the inductive or analytic method Ogston considers the processes of observation, comparison and analogy, and the numerical method. Under the deductive or synthetic method he considers first the process of analysis for deductive purposes, then the process of ratiocination and of verification. He discusses, among the processes subsidiary to induction, such matters as simple observation, experiment, hypothesis,

analogy, the numerical method, terminology and classification. Ogston denounces the current nosologies as obstructive and inelastic and devotes special attention to what he calls the fallacies of non-observation as opposed to the fallacies of mal-observation. Much of this suspicion of Ogston can be traced in Oesterlen and Sir Gilbert Blane, to say nothing of their masters in logic, John Stuart Mill and Sir Francis Bacon.

Sir Gilbert Blane had, for example, in 1819 spoken of the sources of error in medicine as (*a*) the fallacy and danger of hypothetical and theoretical reasoning as especially demonstrated (according to Blane) in Boerhaave, (*b*) the diversity of constitutions, (*c*) the difficulty of "appreciating the salutary efforts of nature and of discriminating them from the operations of art," (*d*) superstition, (*e*) the ambiguity of language, and (*f*) the fallacy of testimonial.

Much can still be gained, no doubt, from a perusal of such works as those of Sir Gilbert Blane, Oesterlen and Ogston, and still more could doubtless be gained by the physician from a close study of John Stuart Mill and his predecessors in pure logic, but these studies were almost wholly given over with the onset of the evolutionary theory in the late fifties, with the crowding developments of pathology and physiology and especially of the bacteriology of the eighties and the immunology of the nineties of the last century. There has, in fact, crept over us the feeling that logical method is an inheritance of us all in like degree and that whatever we do not know of logic at the outset of medical practice we shall never learn. It is precisely the popular single volume text-books that fail to yield much of practical value to the medical student seeking to perfect himself in the *logic* of diagnosis. The dictum, especially of DaCosta and of his successors in the manufacture of single volume text-books, namely, that the art of medicine consists in observation, has apparently abolished the necessity of logic. Carried away by the magic of this word "observation," many authors of physiologic works dealing with the most intricate discussions and fine-drawn conclusions cheerfully called their inductions and deductions by the term "observations." The obvious fact is that diagnosis does not consist in observation at all. Diagnosis requires observation, proceeds upon a basis of observation, but is in itself a process of combination,

of reasoning, of calculation, or of some higher kind of intellectual process which takes observation for granted, uses and chooses among observations, but in no whit makes them.

Among the methods tabulated above I have first set down, following many of the books, *diagnosis by inspection*. Here, at the outset, it may be inquired: "Are we not terming a method of diagnosis what is nothing but a method of observation?" This I freely concede. The names of diseases are achieved by a process of inspection. The result is what we term a diagnosis, but the process by which the so-called diagnosis or disease-name is arrived at is not a process of reasoning at all, but (as stated above) a process akin to the statement, *It is raining*, or *The engine is skipping*. In short, no process of diagnosis in the logical sense is here being used. A diagnosis or disease-name is achieved, but reasoning is not employed. It is only, then, by courtesy that we include inspection under the process-types. The diagnosis follows the inspection as night follows day, or as black follows white, or as man follows woman. The process is one of association of a perfectly simple type. This kind of so-called diagnosis can be made by laymen often as well as by physicians. I am afraid that the ideals of many medical teachers, as they are got by the eager students, consist in teaching them thumb rules of inspection rather than the more tedious and complicated methods of diagnosis. I recalled above how DaCosta spoke of diagnosis by exclusion as a tedious method.

The second method tabulated above is one that I have presumed to term the method of *diagnosis by expectation*. We are familiar with the so-called expectant treatment in therapeutics, but, so far as I know, attention has not been called to the method of diagnosis by expectation. This is, of course, particularly employed in the fulminating, acute diseases on the one hand and the chronic diseases on the other. In the one instance there may not be facts enough to permit a diagnosis by inspection and there may not be time enough to permit elaborate comparisons; accordingly, diagnosis goes by the board until an autopsy either is or is not made. As for the slow, hesitating course of certain diseases, the Micawber attitude is still easier to assume.

I suspect that the method *by induction* is commonly employed

in a manner not far removed from the process of expectation. This method by induction, unlike the method by expectation, is mentioned in the classical works, and also in the modern work of Bieganski. One concludes that the patient looks tuberculous. Here is the suggestion of a diagnosis by inspection. Perhaps one is an office practitioner and time forbids exactitude. One examines the pulmonary apex and discovers suspicions of dullness. One requests the sputum and proceeds to a positive diagnosis of tuberculosis on the basis of tubercle bacilli found in the sputum. Here is a successful case of diagnosis by induction by a sort of skipping of intermediaries (to use James's phrase) and by the least possible work. If the diagnosis is successful, well and good! If unsuccessful, one must proceed to more elaborate methods. It is always possible, too, that the patient may have been suffering from a combination of two or more diseases and that the tuberculosis, *e. g.*, found may be the lesser of two important conditions. One ought not, and I do not, condemn this method by induction just because it is not time-consuming and just because it does not succeed in all cases. In the hands of the expert the method of diagnosis by induction (as the phrase is here used) and the method of diagnosis by inspection are highly commendable methods. In a pragmatic age one ought not to denounce them. From the standpoint of a medical student, however, it would seem wise not to dazzle him with the brilliancies of inspection and induction (in the above narrow sense), but one ought to expound to him the nature of the more complex methods which he must often use in cases that are themselves at all complex.

The methods of *diagnosis ex juvantibus* and *ex nocentibus* tabulated above are in a sense experimental methods of diagnosis on all fours with the method by induction. The diagnosis of syphilis by the administration of antisyphilitic drugs and the procuring of a cure or an alleviation of symptoms is an example of diagnosis *ex juvantibus*. The provocative Wassermann reaction upon the administration of salvarsan is an example of the method of diagnosis *ex nocentibus*. It would be a mistake to consider the administration of drugs for these purposes therapeutic. The methods are methods of diagnosis purely.

Dismissing the methods of inspection, expectation, induction, *ex juvantibus* and *ex nocentibus*, we come to the methods of *diagnosis by comparison*, to which I hope to point out a small addition or modification which I conceive to be of value. Earlier in my communication I have sufficiently discussed these methods and I pointed out the necessity under which we labor of using the method of diagnosis by exclusion in cases where there are no indicator symptoms or presenting symptoms (to use Cabot's phrase for certain indicator symptoms). I wish to illustrate this method of *diagnosis per exclusionem in ordine* from the field of mental diseases, rehearsing the main groups of a practical key[24] which has been built up on the basis of Psychopathic Hospital data.

In passing, I may say that psychiatrists are far more at one in the matter of diagnosis than the general medical man is apt to believe. The unanimity in point of view is far greater than one would suspect from certain nomenclatural differences. The nomenclature of psychiatry is by no means as fixed at the present writing as the nomenclature of dermatology. Yet the unanimity of psychiatrists concerning the major groups of mental disease is, I make bold to say, almost as great, if not quite as great, as the unanimity of dermatologists concerning their main groups. The specialists in psychiatry have for some years past been much interested in proposals of the American Medico-Psychological Association to secure a thorough and acceptable classification of mental diseases to which the State institutions for the custodial insane could conform. The classification adopted by the Medico-Psychological Association in 1917 is, in general, a highly acceptable one.[25] Probably no member of the committee charged with making the classification is entirely satisfied with it in details. Some diagnosticians go so far as to say that in the interest of the patient no classification in the sense of the statistical tables of institutions is worth while, since every instance of mental disease is virtually *sui generis*. There is, of course, much truth in this contention, and the good therapeutist never forgets this fact, borne in upon the mind as it is by the tremendous individual variety of the psychogenic reactions of the individual as such. I found that most of the leading American text-books of psychiatry were also practically at one in the major categories, despite perturbing difficulties in terminology.

The task of the Psychopathic Hospital, dealing as it does not merely with custodial insane but with all the penumbra of "near-insane," of incipient, mild and curable cases, and with many psychoneuroses which would not ordinarily be classed among the insanities, is a somewhat broader and deeper task in diagnosis than that of the custodial institutions for the insane. The Psychopathic Hospital stands as a sort of vestibule between the community and the custodial institutions. From its meshes go back into the community numerous cases whose psychopathia is not far advanced enough to go through the interstices. Not only insanity in the narrow sense, but a variety of other conditions of the *non compos mentis* group, namely, feeble-mindedness, epilepsy, and even many forms of alcoholism, come within the purview of the Psychopathic Hospital. The task of rapid diagnosis was one which had never faced the custodial institution for the insane, because to the latter flowed only cases in which diagnostic experts had made their decision outside the walls of the institution and with the concurrence of the Courts. It became necessary, therefore, to contrive more rapid methods of handling cases than had formerly been available, inasmuch as keen and mature experts were not available for the great run of cases (the Psychopathic Hospital ran the number of voluntary cases and of so-called temporary care group of cases up by the hundreds as soon as it was founded). Some provision had to be made whereby younger men could make reasonably accurate primary siftings of the cases. The rapid development of mental hygiene stole away the young men from our staff at such a rate that provision had to be made for shifting staffs of relatively inexperienced persons. The situation was not unlike that which faced the army itself at the outset of the first draft.

Mental diseases have no indicator symptoms, barring a few, and indeed a very few, so-called pathognomonic symptoms. Psychiatry was devoid of pointers, such as would be available to the specialist in the exanthems, for example. In the absence of indicator symptoms, some method had to be chosen by which every case would have every major hypothesis concerning its nosological grouping raised at some time during his hospital stay. The legal details and official regulations were such that these hypotheses had to be

raised within a very short period. Early in our experience the laws and regulations were such that some kind of diagnosis permitting proper disposition of the case had to be made within four or five days. This proved to be too brief a period in which to make proper disposition and the Temporary Care Law, under which the majority of Psychopathic Hospital cases are admitted for observation directly from the community (without court process), was modified so that a period of seven or eight days is now available. Official disposition is at present made in a total period of ten days, instead of in a total period of seven days; but in practice the external conditions of transfer to social adjustment take from two to three days, so that the total time available for group diagnosis is now a period of from seven to eight days. During this period of seven to eight days what can be done?

I assume that in private practice it may not be necessary to secure the Wassermann reaction of the serum in each and every mental case. For my part, I never feel certain of the diagnosis unless this precaution is taken. In any event, in Psychopathic Hospital practice, with the varying conditions of staff and history standard, it shortly proved necessary to get the Wassermann data from the serum in each case. Only a few of the more conservative hospital superintendents failed at first to approve this plan. The Danvers Hospital in Massachusetts and the hospitals in Michigan, under the influence of the Psychopathic Ward at Ann Arbor, had early adopted doing the Wassermann reaction of the serum as routine. Upon reflection, I found that the proper disposition of almost each and every case depended upon our securing this Wassermann data. If the Wassermann data were dubious, then a longer period of diagnosis was necessary. If the serum proved negative but there were other signs of organic disease of the nervous system, lumbar puncture was resorted to, with the diagnostic hope that the Wassermann reaction and the other reactions of the fluid would prove decisive. The practical disposition of each case I found to depend upon taking the Wassermann reaction of the serum. Accordingly, although there is no indicator symptom which is infallible or anywhere near infallible in the detection of neurosyphilis, the value of the Wassermann reaction of the serum is such that I feel entitled to place the

syphilopsychoses, or mental diseases of syphilitic origin, at the head of all diagnostic consideration. This was the beginning of the plan of ordinal exclusion, the plan of diagnosis *per exclusionem in ordine*. The first thing to be excluded in the diagnosis of mental disease was, in short, syphilis.

The second thing to be excluded was, I found in practice, some form of feeble-mindedness. To be sure, the obvious imbeciles and idiots may secure their diagnosis by inspection, and not so much difficulty is ordinarily felt among the morons or the feeble-minded proper of the English classification. But when one came to the so-called stupids or subnormals, that we now find to lie between the morons below and the normals above, the value of the Binet-Simon tests or their analogues became extreme. One does not need to claim 100 per cent. values for these tests any more than for many another biological test. The tests are nevertheless of value. I found that in practice I needed to know for every lucid case, that is, for every case which could practically be tested metrically, the intellectual titer. Even were I dealing with such a condition as dementia precox or manic-depressive psychosis, I nevertheless found that I needed the mental test as a base line.

Thirdly, I found that the hypothesis of epilepsy or epileptic symptoms and of epileptoid phenomena is one very apt to be isolated from consideration by the tyro or even by the expert. I placed epilepsy third in the diagnostic order of exclusion partly because of the relative reliability of the clinical histories in these cases.

After Group I, the syphilopsychoses, Group II, the hypophrenoses (feeble-mindednesses), Group III, the epileptoses, Group IV, the pharmacopsychoses (including mental diseases due to alcohol, drugs and poisons), I come to Group V, the group of mental diseases due to focal brain disease—the so-called encephalopsychoses. This is the group of cases in which we unconditionally need the data of the routine neurologist's diagnosis. We need to exclude conditions of heightened intracranial pressure and conditions of asymmetry, reflexes and the like, indicating focal brain disease.

Sixthly, after Group V, the encephalopsychoses or neurologist's group, I found that in practice I was asking for the data of the internes, namely, the data which would go to make a diagnosis of

a mental disease somewhere in the "symptomatic" group—Group VI, a group I have termed the somatopsychoses.

After these I tried to exclude presenile and senile phenomena belonging in a group which I have termed, following Nascher's Geriatrics, the geriopsychoses (Group VII).

Then come the stock difficulties of diagnosis for the psychiatrist—the diagnosis of Group VIII, the dementia precox group, which I like to term (from their main symptom as defined by Bleuler) the schizophrenoses.

After the schizophrenoses stand Group IX, the cyclothymoses, or a group including the manic-depressive psychoses and similar mental diseases.

The last of the ten well-defined groups is the familiar group (X) of the psychoneuroses including the hysterias, neurasthenias and psychasthenias, but if in the diagnostic order of exclusion one could not place one's case in any one of these ten comparatively well-defined groups, one would not throw it altogether out of the psychiatric lists, but would call it a plain psychopathia and put it in Group XI, the psychopathoses. Following is a table of these major groups:

MENTAL DISEASE GROUPS (ORDERS)

1.	Syphilitic	Syphilopsychoses
2.	Feeble-minded	Hypophrenoses
3.	Epileptic	Epileptoses
4.	Alcoholic, drug, poison	Pharmacopsychoses
5.	Focal brain ("organic," arteriosclerotic)	Encephalopsychoses
6.	Bodily disease ("symptomatic")	Somatopsychoses
7.	Senescent, senile	Geriopsychoses
8.	Dementia precox, paraphrenic	Schizophrenoses
9.	Manic-depressive, cyclothymic	Cyclothymoses
10.	Hysteria, psycho-, neurasthenic	Psychoneuroses
11.	Psychopathic, paranoiac, et al.	Psychopathoses

I have spoken of the botanical and zoölogical analogues of this grouping in a paper read before the Neurological Association in 1917. Two words of warning are necessary concerning this analogy. The choice of the ending *-osis* is obviously an attempt to get a medical analogue for the botanical ending *-aceæ* or *-osæ*, as in the orders *Rosaceæ* and *Leguminosæ*. These botanical orders are, as is well known, susceptible of splitting into genera and species. It would be an entirely superficial objection, for this account, to say that the

term "species" has obtained in natural history a very special meaning which could not appropriately be given to a disease. Biologically speaking, a species is sometimes taken to mean such a group of plants or animals as are capable of breeding true to type. However, the genus-species distinction is a great deal older than natural history and is used throughout every province of logical classification known. For example, the mineral kingdom, though without process of breeding, is in part susceptible to a classification of the genus-species sort. For that matter, it is not necessary to use the terms order, genus and species for these groupings at all. One might use entirely other distinctions, and still the process of classification might be entirely valid.

The other point which should be made is a kindred one. In zoölogy and botany one would ordinarily be satisfied if in the process of logical exclusion one arrived at the animal or plant which fulfilled the conditions of differentiation, but in the process of diagnosis *per exclusionem in ordine* as applied to mental disease one unconditionally needs to go through the entire list in each case.

For example, one might easily face an instance of mental disease such that the victim was a syphilitic, feeble-minded, epileptic, alcoholic old man, with focal brain disease and somatic disease, the whole contributing to his mental picture. He might conceivably have been psychoneurotic or cyclothymic in his life, for these conditions are doubtless consistent with a fundamental feeble-mindedness in some cases. Whether he could also have been a victim of schizophrenia (dementia precox) and still have mental phenomena attributable to all these other groups is a question. We are aware of cases that start by being feeble-minded and apparently have their schizophrenic process grafted upon them; but whether these combinations of psychoses in so multiplex a form are common or really exist is not my point. Combinations of two or three of these conditions are not infrequent. It is, therefore, stringently necessary, in the rough analysis of psychiatric cases, to make all of these major hypotheses and dismiss them or fix upon them one by one. In short, diagnosis *per exclusionem in ordine* does not necessarily exclude ten out of the eleven groups, but it does endeavor to exclude each one of at least ten of the groups. If the process has succeeded

in excluding the first ten, the case, if psychiatric at all, must remain in the unresolved or ragbag group of psychopathias, Group XI, the psychopathoses. I do not intend here to enter the minutiæ of psychiatric diagnosis, although in another place I have made some endeavor to describe the main genera and species of the groups above tabulated.[26] Incidentally, I have endeavored to place genera and species in the same sort of practical order so that the tyro may consider the diagnosis of the species of syphilitic, hypophrenic and other forms of disease in arbitrary order.

It is scarcely necessary for me to insist that I do not attach great consequence to there being ten or eleven more or less major groups of mental disease. In fact, I insist that the future must interpolate or extrapolate*re* these groups. The groups are not groups based upon clinical resemblances alone, upon anatomical disease, or upon etiology. They are practical groups devised upon what has been found to be the best practical order of exclusion of major groups of mental disease, each seeming to require a special form of handling. I have described the method in my paper entitled, "A Key to the Practical Grouping of Mental Diseases." I am not sure that I would not be warranted in using the term pragmatic instead of practical, for the end and aim of these groupings is, after all, a therapeutic one. The basis for these rough distinctions is a question of disposal of the patient. If the patient belongs among the syphilopsychoses, then antisyphilitic therapy is indicated, or at least must be thought of. If the patient is hypophrenic, then a school for the feeble-minded, an institutional equivalent, or some form of supervision looking to the safeguarding of the community and the development of the case must be adopted. If the case is epileptic, certain special safeguards are necessary, whether the case is an alcoholic epileptic or a traumatic epileptic. The etiology and the anatomy are not at all so much to the point as the practical handling of the epileptic. So, too, with the alcohol and drug cases. In fact, the practical consequences of placing one's patient in one of the first four groups of syphilitic, hypophrenic, epileptic and alcohol or drug cases are such that I think on these practical grounds alone it would be wise for the diagnostician to consider syphilis, feeble-mindedness, epilepsy and alcohol, drugs and poisons before he comes to the

minutiæ. He will thus get settled in his mind many of the practical social questions of a legal, institutional and social service nature. Take the group of mental diseases due to focal brain disease. Should the phenomena of the present war show us that the traumatic psychoses, that is, psychoses due to structural brain disorder, form a practical group on a level of practical interest equal to that of the listed groups, I for one should have no objection to raising these traumatic psychoses, which I at present place under the encephalopsychoses, to a higher dignity, namely, that of the traumatopsychoses. For the moment, I seem to feel, and I suppose most of my colleagues would agree with me, that the traumatic psychoses rather resemble genera under the focal brain disease group than the true great orders of disease. Let the list be telescoped or accordeonized as you will, no damage is done to the concept-value of the greater groups of mental disease.

Again, should someone wish to consider the somatopsychoses ahead of the focal brain disease group and exclude, *e. g.*, pellagra and cardiorenal disease from a role in the given patient ahead of brain abscess, brain tumor, arteriosclerosis, and the like, I should have no objection. The point I make is that some order, not any particular order, is desirable for the tyro in diagnosis. I insist, therefore, on no particular great groups, but on the principle that there should be great pragmatic groups of mental disease analogous to the orders of botany. I insist, again, on no particular order of exclusion, but on some order of exclusion of these groups, and above all, I insist upon subjecting each mental case, so long as indicator symptoms are so wofully absent, to the hypothesis of his possibly belonging under every one of these great groups. Indeed, I feel that he may belong in two or more of these groups.

Whither, you may ask, does the pragmatic principle then disappear? Suppose a man is both epileptic and alcoholic; shall we classify him as in the group of epileptoses or in the group of the pharmacopsychoses? All specialists will remember acrimonious discussions of this nature. Are we dealing with epilepsy or with alcoholism, or with both? Now, I find that in practice, if you couch the question pragmatically, there is rarely, if ever, any doubt into what group you wish to throw your case. Once you put the question

thus: Do you wish to send this case to an institution for epileptics or do you wish to put him in an institution for alcoholics or under appropriate supervision suitable for alcoholics?, there is almost never any doubt on the part of the careful physician whether his case is a case for an institution for epileptics or a case for an institution for alcoholics. The pragmatic question is forthwith settled. The academic question, whether one is an epileptic alcoholic or a alcoholic epileptic becomes a vividly practical question, when the pragmatic, that is to say, the therapeutic, question is raised. I find that this kind of consideration matures the tyro in psychiatry very fast.

Summary. 1. The writer apologizes for a communication on Medical Logic in general when he is only a psychiatrist and but recently a pathologist. His excuse is the necessity for reasonably accurate snap diagnosis in the sifting problem of the psychoses, psychoneuroses and psychopathias, as they flow through the Psychopathic Hospital clinic in Boston.

2. The medical student is found destitute of the ability to define entities and symptoms. The text-books in medicine, especially the single volume text-books, rather tend to make the student believe that diagnosis is observation. In point of fact, diagnosis is not observation, though it requires and indeed stands or falls by accurate observation.

3. DaCosta and his successors have lauded so-called direct diagnosis to the skies and DaCosta rather decried indirect diagnosis by exclusion as a tedious process. An example is cited from DaCosta which shows how relatively simple the classical diagnoses of general medicine are beside those of psychiatry.

4. It seemed that diagnosis by exclusion ought to be rehabilitated. An examination of recent research work in logic indicated that higher and more complex methods than those of observation had become necessary in science. For example, Cabot and Herbert French have attempted to profit by the statistical method, which again, though it requires reasonably accurate observation, is not in itself a method of observation at all. Yet Cabot's statistical frequency tables possess a certain diagnostic value. But the student is often misled by the brilliancies of so-called observational diagnosis

in a clinic. Here diagnoses are often rendered on inspection by a process akin to the recognition of a fruit as an orange, or an automobile trouble as "the engine is skipping." This process is not diagnosis; it is a process of recognition that may receive a simpler term, *gnosis*.

5. The offhand snap diagnostic work at the Psychopathic Hospital indicated that we were in practice relying upon the successive exclusion of certain great disease groups in a certain definite order.

6. A study of Royce's summary of recent researches in logic shows how an organized combination of theory and experience is the higher logic to which the more complicated sciences must resort. Royce himself mentioned psychiatry as a science about to climb out of the classifying era into the era of logical order, that is, of the organized combination of theory and experience. Such a dictum that "disease is life under altered conditions" appears now childishly simple. The idea that disease is a matter of an organism plus a germ was found to be altogether too simple when in the nineties of the last century the concepts of immunology were developed.

7. Those departments of medicine in which the presenting symptom of Richard Cabot is of value are lucky departments. Those departments of medicine in which the indices of disease, or indicator symptoms of the elder writers are available, are also fortunate departments in comparison with psychiatry. In mental disease there are exceedingly few indicator symptoms.

8. Hence the need became apparent of a process of exclusion of great groups or phenomena in a certain definite order, so that nothing of large significance should evade consideration. To avoid the tediousness of exclusion, complained of by DaCosta, the phenomena of disease had to be logically grouped in certain great groups, and the process types of diagnosis in the books may be counted as six or eight, according to definition.

9. In the body of the paper, a special statement was made about each of these process types: Inspection (regarded as not really diagnosis but as merely recognition of gnosis), Expectation, a newly named but frequent method (far older than Micawber), Induction, *Ex juvantibus*, *Ex nocentibus* (three methods in which in no very

rigorous way experiment is used) and three methods of diagnosis by comparison are successively discussed.

10. The ninth method, diagnosis *per exclusionem in ordine*, is in one sense a minor modification of the old method of diagnosis by exclusion. It is of value in departments of medicine where there are no indicator symptoms, and where the so-called presenting symptom would merely indicate some kind of mental disease.

11. The general application of the method of diagnosis *per exclusionem in ordine* in the field of mental disease is demonstrated in the eleventh group of mental diseases into which most of the phenomena may be pragmatically cast. The groupings are not by clinical resemblances, by anatomical attack or by etiology. The distinction is a pragmatic and therapeutic one and will naturally tend to become more and more etiologic as the causes are determined. But in the field of mental disease, causes are so apt either to be unknown or to be multiple that etiological classification on any simple basis such as that of the infectious diseases is practically inconceivable.

12. It is hoped that other departments of medicine (where diagnosis is raised above the level of mere recognition) and where there are few or no pathognomonic or indicator symptoms, will find it to their advantage to set up a method of diagnosis *per exclusionem in ordine*, the great groups or orders being always determined on a pragmatic basis. In the body of the paper are given the general designations of the ten great groups of mental diseases, with the eleventh residual group.

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THE COMPARATIVE FOOD VALUE OF PROTEIN, FAT AND ALCOHOL IN DIABETES MELLITUS, AS MEASURED BY THE NITROGEN EQUILIBRIUM

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In a previous publication[1] it was claimed that probably the lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium of the patient. The experiments reported at that time showed that on a so-called carbohydrate-free diet, in which the proteins and fats were approximately equal to each other, gram for gram, maintenance, as measured by the nitrogen balance, was obtained at from 1500 to 2000 calories, the variations usually depending upon the size and the sex of the patient. No attempts were made to determine which of the ingredients of a starch-free dietary, fat, protein or alcohol was the most efficient protein sparer. In order to administer a diet of as low caloric value as possible and still establish maintenance, it is essential to have this information.

The aim of the present investigation is to determine the comparative value of protein, fat and alcohol as nitrogen sparers, when added to the carbohydrate-free diet in diabetes mellitus. The cases observed were given diets of a constant protein, fat and starch content, and of such caloric value that there was a negative nitrogen balance.

[1] Mosenthal, H. O., and Clausen, S. W.: Archiv. Int. Med., 1918, xxi, 269.

TABLE I.—DETAILED DATA FROM THE OBSERVATIONS ON A CASE OF DIABETES MELLITUS; MALE, AGED FORTY-SEVEN YEARS, HEIGHT 177 CM. THIS IS AN EXAMPLE OF THE EXPERIMENTS AS CARRIED OUT IN EACH OF THE CASES, A SUMMARY ONLY BEING PRESENTED IN TABLES II AND III.

Date.	Urine.			Feces. Nitrogen gm.	N Output, gm.	N Intake, gm.	N Balance, gm.	Food, gm.[1]				Calories.			Weight, kg.
	Glucose, gm.	Acetone bodies as β-oxy., gm.	Nitrogen, gm.					Protein.	Fat.	Carbohydrate.	Alcohol.	Total.	Per kg. per day.	Per sq. m. per hour.	
April 2, 1918	0	9.03	10.08	1.42	11.50	11.50	0	71.9	70.3	12.7	0	1001	19.3	25.6	51 9
April 3, 1918	0	20.57	12.57	1.42	13.99	11.42	−2.57	71.4	70.5	12.6	0	1000	18.9	25.3	52.9
April 4, 1918	0	19.46	10.25	1.42	11.67	11.47	−0.20	71.7	70.3	12.7	0	1000	18.7	25.1	53.6
April 5, 1918	0	25.74	17.03	1.42	18.45	11.46	−6.99	71.6	70.4	12.6	0	1000	19.0	25.4	52.5
April 6, 1918	0	20.91	12.94	1.42	14.36	11.47	−2.89	71.7	70.2	12.9	0	1000	19.2	25.3	52.0
April 7, 1918	0	13.01	12.57	1.42	13.99	11.41	−2.58	71.3	70.7	12.3	0	1000	19.6	24.1	50.9
April 8, 1918	0	16.20	11.52	2.73	14.25	11.50	−2.75	71.9	70.4	12.3	71.4	1500	29.4	38.7	51.0
April 9, 1918	0	8.50	11.22	2.73	13.95	11.39	−2.56	71.2	70.8	12.2	71.4	1500	29.7	38.5	50.5
April 10, 1918	0	11.00	10.14	2.73	12.87	11.47	−1.40	71.7	70.3	12.6	71.4	1499	29.6	38.5	50.6
April 11, 1918	0	8.65	12.60	2.73	15.33	11.46	−3.87	71.6	70.4	12.7	71.4	1500	30.4	39.2	49.3
April 12, 1918	0	6.40	7.63	2.73	10.36	11.46	+1.10	71.6	70.5	12.3	71.4	1499	30.8	39.8	48.7
April 13, 1918	0	6.19	10.76	2.73	13.49	11.41	−2.08	71.3	70.8	12.2	71.4	1501	30.0	39.0	50.0
April 14, 1918	0	4.39	9.52	1.99	11.51	11.36	−0.15	71.0	**125.1**	12.1	0	1504	30.3	39.3	49.5
April 15, 1918	0	6.79	12.10	1.99	14.09	11 36	−2.73	71.0	**125.0**	12.0	0	1503	30.1	39.0	49.9
April 16, 1918	0	6.83	10.74	1.99	12.73	11.36	−1.37	71.0	**125.4**	12.0	0	1507	30 7	39.4	49.1
April 17, 1918	0	6.04	11.36	1.99	13.35	11.38	−1.97	71.1	**125.2**	12.0	0	1505	31.2	39.6	48.8
April 18, 1918	0	5.29	11.39	1.99	13.38	11.38	−2.00	71.1	**125.1**	12.0	0	1504	30.8	39.9	48.7
April 19, 1918	0	7.88	13.95	1.99	15.94	11.39	−4 55	71.2	**125.0**	12.1	0	1504	30.6	39.3	49.2
April 20, 1918	0	8.40	13.95	2.66	16.81	24.00	+7.39	**150.0**	89.2	13.3	0	1499	31.1	39.6	48.7
April 21, 1918	0	10.93	14.65	2.66	17.31	24.02	+6.71	**150.1**	89.3	13.4	0	1501	31.0	39.6	48.4
April 22, 1918	0	5.05	11.97	2.66	14.63	24.05	+9.42	**150.3**	89.1	13.3	0	1499	31.2	39.6	48.0
April 23, 1918	0	8.17	12.58	2.66	15.24	24.02	+8.78	**150.1**	89.4	13.1	0	1501	30.7	39.9	48.7
April 24, 1918	0	9.31	11.29	2.66	13.95	24.02	+10.07	**150.1**	89.4	13.2	0	1501	31.3	39.7	47.9
April 25, 1918	0	5.67	11.09	2.66	13.75	24.02	+10.27	**150.1**	89.5	13.1	C	1502	30.1	39.9	48.7

[1] The articles of food printed in heavy type indicate the addition to the control diet.

TABLE II.—CONDENSED DATA FROM CASES OF DIABETES MELLITUS ON CARBOHYDRATE-FREE DIETS, SHOWING THE COMPARATIVE VALUE OF PROTEIN, FAT AND ALCOHOL AS NITROGEN SPARERS. THE DAILY FOOD WAS CONSTANT DURING EACH PERIOD.

Patient.	Period, days.	Glycosuria, gm. per day.	Nitrogen, gm. per day.			Food, gm. per day.[1]				Calories.			Acetone bodies in urine β-oxy., gm. per day.
			Intake.	Output (urine and feces).	Balance.	Protein.	Fat.	Carbohydrate.	Alcohol.	Total per day.	Per kilo per day.	Per sq. m. per hour.	
Case 1	6	0	11.4	14.2	−2.8	71.4	70.5	12.3	0	999	14.3	23.0	12.7
Med. history, No. 39566	6	0	11.4	14.4	−3.0	71.5	70.4	12.4	71.4	1499	21.4	34.5	12.7
Male, aged sixty-three years	6	0	11.4	11.9	−0.5	71.3	125.1	12.1	0	1505	21.5	34.7	8.0
Height, 170 cm. (5 ft. 7 in.)	6	0	11.5	12.4	−0.9	71.7	70.6	12.4	0	1001	14.3	23.0	9.4
Weight, 70 kg. (154 lbs.)	6	0	11.4	13.7	−2.3	71.1	125.2	12.1	0	1506	21.5	34.7	9.9
	6	0	11.4	13.9	−2.5	71.4	70.5	12.4	71.4	1499	21.4	34.5	10.5
	6	0	24.1	18.3	+5.8	150.3	89.3	13.5	0	1502	21.5	34.6	9.8
Case 2													
Med. history, No. 39538	6	0	11.5	14.0	−2.5	71.6	70.4	12.6	0	1000	20.0	25.8	18.1
Male, aged forty-seven years	6	0	11.4	13.4	−2.0	71.5	70.5	12.4	71.4	1499	30.0	38.7	9.5
Height, 177 cm. (5 ft. 10 in.)	6	0	11.4	13.5	−2.1	71.1	125.2	12.0	0	1505	30.1	38.8	6.2
Weight, 50 kg. (110 lbs.)	6	0	24.0	15.3	+8.7	150.1	89.3	13.2	0	1500	30.0	38.7	7.9
Case 3	6	0	11.4	14.4	−3.0	71.5	70.5	12.4	0	1000	19.2	25.9	
Med. history, No. 39300	6	0	11.5	13.8	−2.3	71.6	70.5	12.5	71.4	1500	28.9	38.9	8.8
Male, aged twenty-two years	6	0	11.4	14.3	−2.9	71.4	125.2	12.2	0	1507	29.0	39.0	7.2
Height, 172 cm. (5 ft. 8 in.)	6	0	11.4	12.7	−1.3	71.5	70.4	12.8	0	1000	19.2	25.9	9.9
Weight, 52 kg. (114 lbs.)	6	0	24.0	25.1	−1.1	150.2	143.2	13.3	0	2002	38.5	51.9	9.3
	6	0	24.1	24.9	−0.8	150.4	143.2	25.3	0	2053	39.5	53.2	11.2
Case 4	6	0	11.5	12.1	−0.6	71.6	70.5	12.5	0	1000	16.7	23.9	
Med. history, No. 38448	6	0	11.4	13.3	−1.9	71.5	70.4	12.4	71.4	1499	25.0	35.8	10.2
Male, aged thirty-three years	6	0	11.4	12.9	−1.5	71.2	125.2	12.1	0	1506	25.1	36.0	8.8
Height, 177 cm. (5 ft. 10 in.)	6	0	24.0	19.1	+4.9	150.2	89.2	13.5	0	1501	25.0	35.8	12.3
Weight, 60 kg. (132 lbs.)													
Case 5	3	0	11.6	14.3	−2.7	72.2	70.2	12.2	0	999	21.3	28.1	
Med. history, No. 39079	6	0	11.6	13.3	−1.7	72.5	70.2	12.4	37.6	1264	26.9	35.5	
Male, aged fifty-nine years	6	0	11.6	13.3	−1.7	72.2	70.3	12.1	0	999	21.3	28.1	
Height, 163 cm. (5 ft. 4 in.)	6	0	11.4	10.2	+1.2	71.3	125.4	12.1	0	1508	32.1	42.4	
Weight, 47 kg. (103 lbs.)	6	0	11.4	11.9	−0.5	71.4	125.3	12.6	37.6	1773	37.7	49.8	
	6	0	24.0	18.4	+5.6	150.2	89.4	13.1	0	1501	31.9	42.2	
	6	0	11.5	14.9	−3.4	71.7	70.3	12.5	37.6	1262	26.9	35.5	
	6	0	11.4	12.1	−0.7	71.2	125.1	12.1	0	1505	32.0	42.3	
	6	0	11.4	12.5	−1.1	71.3	70.4	12.8	0	1000	21.3	28.1	
	6	0	24.1	21.5	+2.6	150.6	89.2	13.4	0	1502	32.0	42.2	
	6	0	11.4	14.5	−3.1	71.2	125.2	12.1	0	1506	32.0	42.3	
	6	0	11.5	13.7	−2.2	71.6	70.4	12.3	71.4	1499	31.9	42.1	
	6	0	11.4	12.3	−0.9	71.2	125.2	12.2	71.4	2006	42.7	56.4	
Case 6	6	0	11.4	14.4	−3.0	71.5	70.5	12.4	0	1000	17.9	25.0	
Med. history, No. 39254	6	0	11.5	13.8	−2.3	71.6	70.5	12.5	71.4	1500	26.8	37.5	
Male, aged fifty-five years	6	0	11.4	14.3	−2.9	71.4	125.2	12.2	0	1507	26.9	37.7	

Height, 173 cm. (5 ft. 8 in.)	6	0	11.4	12.7	−1.3	71.5	70.4	12.8	0	1000	17.9	25.0	
Weight, 56 kg. (123 lbs.)	6	0	11.4	13.7	−2.3	71.2	**125.3**	12.4	0	1508	26.9	37.7	
	6	0	11.5	14.2	−2.7	71.6	70.5	12.5	**71.4**	1500	26.8	37.5	
	8	0	24.0	20.3	+3.7	**150.1**	89.3	13.3	0	1500	26.8	37.5	
	6	0	24.0	24.6	−0.6	**150.1**	89.5	13.3	**35.5**	1751	31.3	43.8	
	6	0	24.0	21.2	+2.8	**150.1**	**116.2**	13.2	0	1750	31.3	43.7	
Case 7	8	0	11.5	14.4	−2.9	71.8	70.4	12.5	0	1000	25.0	29.6	
Med. history, No. 39176	6	0	11.4	11.9	−0.5	71.5	70.5	12.6	**71.4**	1500	37.5	44.4	
Male, aged twenty-three years	6	0	11.4	10.2	+1.2	71.2	**126.6**	12.4	0	1520	38.0	45.0	
Height, 167 cm. (5 ft. 6 in.)	6	12.0	11.5	12.4	−0.9	71.6	70.6	12.5	0	1001	25.0	29.6	
Weight, 40 kg. (88 lbs.)	4	7.0	11.4	9.7	+1.7	71.4	**125.4**	12.2	0	1509	37.7	44.6	
Case 8	7	0	11.5	13.0	−1.5	71.9	70.2	12.1	0	997	23.2	29.7	
Med. history, No. 38990	7	0	11.4	14.3	−2.9	71.4	70.7	12.2	**37.6**	1263	29.4	37.6	
Male, aged thirty-five years	6	0	11.4	12.7	−1.3	71.3	**125.4**	12.4	0	1509	35.1	44.9	
Height, 158 cm. (5 ft. 2 in.)	6	0	24.1	18.0	+6.1	**150.3**	89.7	13.3	0	1505	35.0	44.8	
Weight, 43 kg (95 lbs.)	6	0	11.4	13.1	−1.7	71.5	70.3	12.5	**37.6**	1261	29.3	37.6	
	6	0	11.5	11.3	+0.2	71.6	70.4	12.4	0	999	23.2	29.7	
	6	0	24.0	18.3	+5.7	**150.2**	89.4	13.5	0	1503	35.0	44.8	
	4	0	11.4	14.8	−3.4	71.4	**125.6**	12.0	0	1510	35.1	44.9	
Case 9	3	0	11.7	12.8	−1.1	73.3	70.4	10.8	0	1000	22.7	28.2	
Med. history, No. 38896	3	0	11.5	13.3	−1.8	71.8	70.4	12.3	**37.6**	1263	28.7	35.6	
Male, aged fifty-two years	3	0	11.4	12.9	−1.5	71.2	70.3	12.3	0	996	22.6	28.1	
Height, 169 cm. (5 ft. 7 in.)	6	0	11.6	12.4	−0.8	72.4	70.2	12.4	**37.6**	1264	28.7	35.6	
Weight, 44 kg. (97 lbs.)	6	0	11.6	12.4	−0.8	72.3	70.4	12.2	0	1001	22.8	28.2	
	6	0	11.4	12.4	−1.0	71.1	**125.3**	11.9	0	1506	34.2	42.4	
	6	0	24.0	19.0	+5.0	**150.2**	89.8	12.0	0	1500	34.1	42.3	
Case 10	6	0	16.9	20.8	−3.9	105.7	105.7	20.6	0	1501	25.4	38.5	15.9
Med. history, No. 39819	6	0	32.1	27.1	+5.0	**200.3**	117.7	20.5	0	2000	33.9	51.3	8.9
Male, aged forty-nine years	6	0	16.9	19.9	−3.0	105.6	105.7	20.5	**71.4**	2000	33.9	51.3	7.5
Height, 162 cm. (5 ft. 4 in.)	6	0	32.1	23.7	+8.4	**200.4**	117.6	20.9	0	2001	33.9	51.3	13.2
Weight, 59 kg. (130 lbs.)	6	0	32.1	26.8	+5.3	**200.6**	117.5	20.7	0	2000	33.9	51.3	18.8
	6	0	32.1	24.5	+7.6	**200.7**	117.6	20.5	0	2001	33.9	51.3	6.0
	9	0	32.1	25.4	+6.7	**200.5**	117.6	20.5	0	2000	33.9	51.3	8.2
Case 11	6	0	11.4	14.4	−3.0	71.3	70.6	12.5	0	1000	13.9	22.2	
Med. history, No. 39818	6	0	24.1	19.5	+4.6	**150.3**	89.2	13.2	0	1500	20.8	33.3	
Male, aged twenty-five years	6	0	24.1	19.0	+5.1	**150.6**	89.1	13.3	0	1501	20.8	33.3	13.78
Height, 176 cm. (5 ft. 9 in.)	6	0	24.0	22.1	+1.9	**150.1**	89.2	13.5	0	1500	20.8	33.3	17.05
Weight, 72 kg. (158 lbs.)	6	0	24.0	23.4	+0.6	**150.2**	89.3	13.2	0	1500	20.8	33.3	10.01
	9	0	24.0	25.3	−1.3	**150.2**	89.3	13.2	0	1500	20.8	33.3	9.47
Case 12	6	0	11.4	15.0	−3.6	71.3	70.5	12.5	0	999	15.1	23.9	
Med. history, No. 39590	6	0	11.4	14.3	−2.9	71.2	**125.2**	12.1	0	1506	22.8	36.0	
Male, aged twenty-six years	6	0	24.0	20.0	+4.0	**150.1**	89.6	12.9	0	1502	22.8	35.9	
Height, 167 cm. (5 ft. 6 in.)													
Weight, 66 kg. (145 lbs.)													
Case 13	6	0	11.5	10.2	+1.3	71.6	70.6	12.7	0	1002	18.9	26.1	9.5
Med. history, No. 39820	6	0	24.0	19.3	+4.7	**150.1**	89.6	13.2	0	1503	28.4	39.1	10.2
Male, aged thirty-three years													
Height, 169 cm. (5 ft. 7 in.)													
Weight, 53 kg. (117 lbs.)													
Case 14	6	2.8	11.2	12.7	−1.5	69.7	**112.7**	9.3	**38.7**	1643	39.1	45.3	
Med. history, No. 39182	6	26.8	21.6	22.2	−0.6	**135.2**	76.1	9.9	**38.7**	1574	37.5	43.3	
Male, aged forty-four years													
Height, 179 cm. (5 ft. 10 in.)													
Weight, 42 kg. (92 lbs.)													

[1] The articles of food printed in heavy type indicate the addition to the control diet.

The fats and proteins were approximately equal to each other, gram for gram; the carbohydrates were those unavoidably present in the green vegetables. This constituted the control period; it was usually kept up for six days. Subsequently, definite amounts of protein, fat and alcohol were added to the dietary and the effect on the nitrogen balance noted. The methods were the same as previously employed. One of the experiments is presented in detail in Table I. All the other cases were studied by similar methods, but only a summary of the findings is given in Tables II and III.

TABLE III.—SUMMARY OF TABLE II, GIVING THE AVERAGE DAILY NITROGEN BALANCE IN GRAMS DURING THE DIFFERENT PERIODS OF FEEDING.

Case No.	Character of period.						
	Control.	Protein.	Fat	Alcohol.	Protein plus fat.	Fat plus alcohol.	Protein plus alcohol.
1	−1.9	+5.8	−1.4	−2.8			
2	−2.5	+8.7	−2.1	−2.0			
3	−2.2	.....	−2.9	−2.3	−1.0		
4	−0.6	+4.9	−1.5	−1.9			
5	−1.8	+4.1	−0.9	−2.4	.....	−0.7	
6	−2.2	+3.7	−2.6	−2.5	+2.8	.....	−0.6
7	−1.9	.....	+1.5	−0.5			
8	−0.7	+5.9	−2.4	−2.3			
9	−1.1	+5.0	−1.0	−1.3			
10	−3.9	+6.0	.....	−3.0			
11	−3.0	+2.5					
12	−3.6	+4.0	−2.9				
13	+1.3	+4.7					
14	.....	.....	.....	.....	.....	−1.5	−0.6

It is very evident from a study of these tables that fat and alcohol when added to a low caloric protein-fat diet have little or no influence in sparing nitrogen; protein, however, has a very positive effect in this regard. These findings are not absolutely constant in all these observations. Thus, case 7 has a distinct retention of nitrogen during the high fat feeding and case 5 (Table II) exhibits the same phenomenon in the first of the three fat periods, but not in the two subsequent ones. There was no exception to the rule that alcohol was of no value as a nitrogen sparer even when it was combined with protein, as in cases 6 and 14, or with fat, as in cases 5 and 14.

With one exception, during a combined fat and protein period in case 3, there was marked retention of nitrogen when a high protein diet was used, and even in the one instance cited there was a diminished loss of nitrogen as compared to the control figures.

Lusk,[1] quoting the work of Thomas and Rubner, shows how the body may maintain nitrogen equilibrium much more readily on a protein-fat diet than on one of protein alone, and how with increasing quantities of fat there is an increasing addition of protein to the body. In the present experiments the latter statement has proved itself to be the exception rather than the rule. The results have been so consistent in this regard that the conclusion seems justified that it may be considered to be of no very great value from the point of view of the addition of nitrogen to the body to increase the fat in a protein-fat diet.

Previous investigations, as summarized by Rosemann,[2] have yielded substantially the same results with alcohol on mixed diets as the present experiments do on protein-fat diets. The addition of alcohol did not spare nitrogen if given for a period of six days. It may be that if the observations had been continued, protein might have been saved to the body by the utilization of alcohol, as was the case in Rosemann's observations. The alcohol, even more constantly than the fat, fails to bring about an assimilation of nitrogen, and is not to be recommended for the dietary of the diabetic if it is desired to spare protein.

The markedly positive nitrogen balances on the "carbohydrate-free" diets with high protein appear to solve the problem of what type of food is best suited to spare protein in the diabetic. The effort produced in these cases may be greater than that seen in normal individuals, inasmuch as most of these patients were either starved or kept on low diets for a considerable length of time before the systematic observations were begun. It has often been noted that it is exceedingly difficult to bring about "a prolonged deposition of protein in the normal adult when fat is given with it."[3] In

[1] The Elements of the Science of Nutrition, 1917, third edition, pp. 254 and 255.

[2] Oppenheimer's Handbuch der Biochemie des Menschen und der Tiere, part I, iv, 436.

[3] Lusk, G.: Loc. cit., p. 255.

the diabetic this apparently is not true for six-day periods at least. Two experiments were conducted in which the high protein feeding was kept up for a longer period in order to illuminate this point. Case 10 (Table II) was still retaining nitrogen at the rate of 6.7 gm. per day at the end of thirty-three days; case 11 (Table II) gave evidences of marked assimilation for twelve days, followed by twelve days in which the nitrogen balance shaded off to terminate in a nitrogen loss in the subsequent period. In summarizing these findings it may be said that a positive nitrogen balance is readily achieved in diabetes on protein-fat diets with a high protein content, and that such an assimilation of nitrogen may persist for a considerable period before nitrogen equilibrium is reached.

It may be of interest to note in a few of these mild or moderately severe diabetics in whom the acid substances were determined in the urine (Table II) that none of the food elements, when increased, whether protein, fat or alcohol, had any apparent effect on the amount of the acetone bodies excreted. This is somewhat at variance with the well-known observations that especially the fats may be responsible for an increase of these substances and alcohol for their diminution. It is probable that the very severe diabetic reacts differently in this regard and that over short periods at least a high fat diet may result in no increase in the acidosis of moderately severe diabetics.

Conclusions. The addition of an equal number of calories of protein, fat or alcohol to a low caloric carbohydrate-free diet in cases of diabetes mellitus results in the assimilation of considerable amounts of nitrogen when the protein is used, a favorable nitrogen balance in only occasional instances with fat and no change in the nitrogen equilibrium when alcohol is given. This would point to a high protein diet as the most advisable low-calory carbohydrate-free diet by which to conserve the body tissues and furnish a maintenance ration for the diabetic.

THE FRACTIONAL EXAMINATION OF THE DUODENAL CONTENTS

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The duodenal contents are of intrinsic value for the welfare of the organism. The main process of digestion is accomplished by the proper working and correlation of the different fluids entering into this comparatively small part of the digestive apparatus (the duodenum). It is quite natural that a study of these secretions from every possible viewpoint will prove useful physiologically as well as pathologically.

In several previous communications I published my results concerning the examination of the duodenal contents. Usually these explorations of the duodenal secretions had been done either in the fasting condition of the patient or some time after the ingestion of either tea and sugar or bouillon. No particular attention had been paid as to the length of time after the meal the examination had been performed.

It appeared to me worth while to undertake a comparative study between the results of the examination in the fasting condition and at different periods after certain test meals. Inasmuch as the duodenal tube must have a comparatively narrow lumen, solid food, even mechanically well comminuted, would be apt to clog up the instrument, and would therefore be inappropriate for these examinations.

For these reasons I had already formerly employed either tea and sugar or bouillon as preparatory meals.

In the present investigation I selected a cup of beef bouillon (one bouillon cube, usually Armour & Co., to one cup of hot water)

as the proper test meal. Beef being a strong stimulant for the digestive secretions seemed to answer well our purpose.

Examination of the duodenal contents was first made in the fasting condition, then a cup of beef bouillon was given by mouth and the duodenal contents aspirated every half-hour for a period of two hours (fractional examination).

In order to have a larger collection of cases, we utilized many patients who were on duodenal alimentation or duodenal fluid instillation for this purpose. In these cases the explorations can be carried out with the greatest ease, for they have the tube already in the right place. But we also took patients not accustomed to the tube, principally in conditions in which the bile or pancreatic secretions had to be examined any way. We also had two persons without any subjective symptoms, representing the normal, who were willing to undergo this examination for the benefit of science (George C. and Miss Ruth M., to whom I express my thanks for coöperation).

In all these additional cases the mode of procedure was as follows: The patient was given the duodenal tube in the evening after a light supper. Attention was paid to the length of tube which had entered the buccal cavity before retiring. Mark III of the tube should have reached the mouth; if not, the patient is given milk or water and the tube in this way made to go in beyond the III mark before going to sleep. In patients who sleep restlessly it is advisable to attach the tube, lying outside the mouth, with a piece of adhesive plaster to the cheek, in order to avoid a pulling out of the instrument during the night by any inadvertent motion. In the early morning the capsule end of the tube has usually reached the duodenum and the desired examination can be performed.

The specimens obtained were examined within one or two hours after aspiration. The quantity and appearance of the fluid, in regard to color and clearness, then the reaction, whether neutral, alkaline or acid, and the figure of alkalinity or acidity, were ascertained. For the reaction, blue and red litmus paper was used, while the degree of alkalinity was determined by titration, with methyl-orange and $\frac{1}{10}$ standard solution of hydrochloric acid. The ferments (amylopsin, steapsin and trypsin) were estimated by

employing agar tubes[1] and gauging the amounts by the digested piece of the agar column, stated in millimeters. I am greatly obliged to Dr. O. Hensel for having examined seven specimens from my cases.

Altogether, I have examined the duodenal contents of thirty-two people with the fractional method. In all the bouillon test meal was used; in most of the patients the duodenal contents were also examined in the fasting condition. It will be best to first give the results of these examinations in table form.

Remarks. The table on pages 314–318 begins with two apparently normal individuals (Group I). In Case 1, R. M., the alkalinity of the duodenal contents in the fasting condition is 30 while one-half hour after the bouillon test meal it is only 10, then it goes to 25, 25 and ultimately to 30. The ferments, likewise, are strongest in the fasting condition while they are weakest one-half hour after the test meal, to increase in strength later on.

Case 2, also belonging to the apparently normal, shows already a different relation. Here the alkalinity in the fasting condition is 20; half an hour after the test meal it is the same. The ferments in the fasting condition are weaker than half an hour after the bouillon; one hour after the test meal they are strongest while later the steapsin ferment grows weaker.

Group II. Five cases with normal gastric secretion, HCl+, acidity 60. In A. M., R. S. and J. M. W. the alkalinity increases up to the end of the first hour, it then slightly diminishes. In Mrs. T. T. and W. B. the alkalinity shows a steady increase up to the end of the two hours.

The ferments show great variations, but, on the whole, their strength, on an average, is greatest about one hour after the bouillon test meal.

Group III. Eleven cases of hyperchlorhydria, in three of which the fasting duodenal contents were examined, show in two a slightly diminished alkalinity one-half hour after the bouillon test meal, while in one there was apparently no difference.

[1] Einhorn, Max: Agar Tubes for the Estimation of the Pancreatic Ferments, Med. Record, January 15, 1910; also Recent Studies of Pancreatic Secretions, Med. Record, January 12, 1915.

TABLE OF CASES IN WHICH FRACTIONAL EXAMINATIONS OF THE DUODENAL CONTENTS WERE MADE.

No.	Name.	Diagnosis.	Gastric contents.	Date and time.	Duodenal contents.					Remarks.
					Quantity and appearance.	Alkalinity.	Amylopsin.	Steapsin.	Trypsin.	
				GROUP I.						
1	Miss R. M.	Apparently normal	½ h. a. b., HCl+; ac., 30 1¼ h. a. b., HCl+; ac., 40	March 3, 1918 Fasting	1½ c.c.; yellow; turbid	30	8	5	5½	
				½ h. a. b.	2 c.c.; straw yellow; slightly turbid	10	4	1	1	
				1 h. a. b.	2 c.c.; yellow; golden tinge; slightly turbid	25	7	3	5	
				1½ h. a. b.	2 c.c.; yellow; turbid	25	6½	4	5	
				2 h. a. b.	2½ c.c.; yellow; slightly turbid	30	7	4	5½	
2	Mr. G. C.	Apparently normal	½ h. a. b., HCl+; ac., 50	Mar. 17, 1918 Fasting	4 c.c.; yellow, very slightly turbid	20	7	Tr.	6	
				½ h. a. b.	6 c.c.; golden brown and clear	20	10	2	7	
				1 h. a. b.	4 c.c.; golden yellow and clear	25	12	2	6	
				1½ h. a. b.	3 c.c.; straw yellow and clear	20	9	1	5	
				2 h. a. b.	6 c.c.; golden yellow	35	12	1	7	
				GROUP II.						
3	Mr. A. M.	Cholecystitis; chronic appendicitis	HCl+; ac., 60	Feb. 21, 1918 Fasting	3 c.c.; turbid; green, yellow	20	10	25	4	
				½ h. a. b.	3 c.c.; turbid; green, yellow	20	9	4	5	
				1 h. a. b.	3 c.c.; yellow; slightly turbid	30	4	0	Tr.	
				1½ h. a. b.	2½ c.c.; yellow; very slightly turbid	10	5	Tr.	1	
				2 h. a. b.	2½ c.c.; clear; straw colored	10	4	Tr.	3	

				Feb. 5, 1918					
4	Miss R. S.	Nervous regurgitation	HCl+; ac., 60	½ h. a. b.	6 c.c.; yellow	5	0	½	½
				1 h. a. b.	6 c.c.; yellow	15	4½	1½	2½
				1½ h. a. b.	2 c.c.; yellow	10	6	1½	1
				2 h. a. b.	1½ c.c.; yellow	10	0	1	Tr.
				Oct. 30, 1917					
5	Mr. J. M. W.	Duodenal ulcer	HCl+; ac., 60	½ h. a. b.	Yellow; cloudy	40	5	½	Tr.
				1½ h. a. b. (boiled)	Yellow; cloudy	40	0	0	0
				1 h. a. b.	Watery; yellow	50	6	2	2
				1½ h. a. b.	Light; yellow	40	10	6	5
				2 h. a. b.	Light; yellow	40	8	4	4
				Oct. 27, 1917					
6	Mr. T. T.	Gastric ulcer	HCl+; ac., 60	½ h. a. b.	Cloudy	10	0	Tr.	Tr.
				1 h. a. b.	Clear	10	7	2	2
				1½ h. a. b.	Clear	15	7	5	6
				2 h. a. b.	Turbid	25	4	2	Tr.
				Mar. 9, 1918					
7	Mrs. W. B.	Gastric ulcer	½ h. a. b., HCl+; ac., 40	½ h. a. b.	4 c.c.; yellowish-green tinge; turbid	15	8	2	4
			1 h. a. b., HCl+; ac., 60	1 h. a. b.	1 c.c.; yellow; slightly tubid	20	8	3	3½
				1½ h. a. b.	½ c.c.; yellow; slightly turbid	25	7½	7	4
				2 h. a. b.	1 c.c.; straw yellow; slightly turbid	25	10	7	5
				Group III.					
				Feb. 10, 1918					
8	Mrs. J. T. P.	Cholecystitis; gastric ulcer	HCl+; ac., 65	Fasting	7½ c.c.; yellow; turbid	40	20	7	4½
				½ h. a. b.	7 c.c.; yellow; turbid	20	12	3	2
				1 h. a. b.	5½ c.c.; yellow; turbid	35	6	2½	4
				1½ h. a. b.	5 c.c.; reddish tinge; sediment	40	5½	1	4
				2 h. a. b.	8 c.c.; light yellow; sediment	40	15	1	5
				Sept. 17, 1917					
9	Mr. C.	Duodenal ulcer	HCl+; ac., 70	½ h. a. b.	6 c.c.; golden yellow	15	6	1½	1½
				1 h. a. b.	7 c.c.; golden yellow	20	6	3	4
				1½ h. a. b.	2 c.c.; golden yellow	25	5	1	2
				2 h. a. b.	4⅛ c.c.; golden dark	30	6	5	5

h. a. b. = hour(s) after bouillon.

TABLE OF CASES IN WHICH FRACTIONAL EXAMINATIONS OF THE DUODENAL CONTENTS WERE MADE—*continued.*

No.	Name.	Diagnosis.	Gastric contents.	Date and time.	Duodenal contents.					Remarks.
					Quantity and appearance.	Alkalinity.	Amylopsin.	Steapsin.	Trypsin.	
			GROUP III—Continued							
				Sept. 30, 1918						
10	Mr. P. D.	Duodenal ulcer	HCl+; ac., 72	½ h. a. b.	Pale green	17½	8	½	1	
				1 h. a. b.	Yellow, green	22½	9	1	1½	
				1½ h. a. b.	Green	10	6	½	1½	
				Mar. 17, 1918						
11	Mrs. L. M.	Enteroptosis; hyperchlorhydria	HCl+; ac., 80	Fasting	1 c.c.; green; turbid	20	8	4	5	
				1 h. a. b.	5 c.c.; greenish yellow; clear	30	7	3	3	
				1 h. a. b.	1 c.c.; yellow, tinge of green; clear	20	9	Tr.	5½	
				1½ h. a. b.	2 c.c.; yellow, tinge of green; clear	30	8	1	6	
				2 h. a. b.	2 c.c.; yellowish green; slightly turbid	25	8	2	6	
				Nov. 21, 1917						
12	Mrs. E. W. G.	Gastric ulcer	HCl+; ac., 80	½ h. a. b.	Turbid	0	0	0	0	
				1 h. a. b.	Turbid	10	5	1	0	
				1½ h. a. b.	Green; turbid	12½	6	1½	2	
				2 h. a. b.	Green; turbid	12½	5	1	1	
				Sept. 27, 1917						
13	Mr. W. E.	Gastric ulcer; nephrolithiasis	HCl+; ac., 80	½ h. a. b.	Colorless; clear	0	0	0	0	
				1 h. a. b.	Yellow; turbid	15	8	½	1	
				1½ h. a. b.	Green; turbid					
				2 h. a. b.	Green; turbid	10	10	½	1	
				Oct. 4, 1917						
14	Mr. I. O.	Gastric ulcer	HCl+; ac., 90	½ h. a. b.	Light yellow	2	3	1	1	
				1 h. a. b.	Light yellow	10	5	1½	1½	
				1½ h. g. b.	Green	15	6	1½	1	
				2 h. a. b.	Green	15	3	½	½	
				Jan. 18, 1918						
15	Mr. M. S.	Gastric ulcer	HCl+; ac., 90	½ h. a. b.	2 c.c. gold yellow	10	2½	1	3	
				1 h. a. b.	4 c.c. gold yellow; clear	20	5	2	2	
				1½ h. a. b.	3 c.c. gold yellow; clear	20	5	2	3	
				2 h. a. b.	2 c.c. gold yellow; clear	10	7	2	2	

				Sept. 19, 1918						
16	Mr. W. F. Mc.	Duodenal ulcer	HCl+; acidity, 90	½ h. a. b.	Yellow	20	4	1	5	
				1 h. a. b.	Colorless	25	3	1		
					Colorless	..	3½	½	2	
					Colorless	..	3			
				Feb. 28, 1918						
17	Mr. C. M. D.	Duodenal ulcer	HCl+; ac., 90	Fasting	½ c.c.; whitish; turbid	..	0	Tr.	Tr.	
				½ h. a. b.	1 c.c.; turbid: yellowish tinge	..	9	1½	2	
				1 h. a. b.	1 c.c.; slightly yellow; turbid	..	5	4	2½	
				1½ h. a. b.	3 c.c.; yellowish-green tinge; slightly turbid	20	8	4	5	
				2 h. a. b.	4 c.c.; yellowish green	30	11	1½	8	
				Feb. 9, 1918						
18	Mrs. H. M. R.	Pyloric ulcer	HCl+; ac., 96	Fasting	4 c.c.; yellow; turbid	20	6½	5½	3	
				½ h. a. b.	5 c.c.; yellow; turbid	15	5½	2½	2½	
				1 h. a. b.	2 c.c.; yellow; turbid	20	9	6	3	
				1½ h. a. b.	1¾ c.c.; yellow; turbid	30	6½	2	4	
				2 h. a. b.	3½ c.c.; yellow; turbid	30	6½	2½	2	
				GROUP IV.						
				Mar. 12, 1918						
19	Mr. J. D.	Duodenal ulcer	HCl+; acidity 35	Fasting	6 c.c.; yellow; turbid	35	5	1	4	
				½ h. a. b.	4 c.c.; yellow; turbid; greenish tinge	30	10	2	4½	
				1 h. a. b.	6 c.c.; straw colored; very slightly turbid	35	9	2½	4	
				1½ h. a. b.	2 c.c.; yellow; very slightly turbid	30	6	1	2	
				2 h. a. b.	3 c.c.; yellow; very slightly turbid	30	7	1½	5	
				Feb. 23, 1918						
20	Mr. M. S.	Probable cholelithiasis; chronic gastric catarrh	HCl+; ac., 35	Fasting	6 c.c.; yellow, green; turbid	15	8	1½	Tr.	
				½ h. a. b.	6 c.c.; yellow, green; turbid	20	14	7	Tr.	
				1 h. a. b.	½ c.c.; straw yellow	..	10	4	4	Urobilinogen
				1½ h. a. b.	¼ c.c.; yellow; clear	..	6	1	1	not present.
				2 h. a. b.	¼ c.c.; yellow	..	Tr.	Tr.	Tr.	

h. a. b. = hour(s) after bouillon.

TABLE OF CASES IN WHICH FRACTIONAL EXAMINATIONS OF THE DUODENAL CONTENTS WERE MADE—*continued.*

No.	Name.	Diagnosis.	Gastric contents.	Date and time	Duodenal contents.					Remarks.
					Quantity and appearance.	Alkalinity.	Amylopsin.	Steapsin.	Trypsin.	
			GROUP IV—Continued							
21	Dr. F. W. H.	Gastric catarrh	HCl?; ac., 20	Mar. 10, 1918						
				Fasting	15 c.c.; greenish; turbid	Ac.	0	0	0	Probably from the stomach.
				½ h. a. b.	10 c.c.; turbid; greenish tinge	Ac.	0	0	0	
				1 h. a. b.	6 c.c.; yellow; clear	20	8	Tr.	3	
				1½ h. a. b.	4 c.c.; yellow; clear	15	8	2	5	
				2 h. a. b.	6 c.c.; straw yellow; slightly turbid	10	6	1	3	
22	Mrs. W.	Cholelithiasis	.....	Mar. 23, 1918						
				Fasting	8 c.c.; golden yellow; very slight turbidity	10	11	3	5½	
				½ h. a. b.	8 c.c.; straw yellow; very slight turbidity	12	9	2	6	
				1 h. a. b.	10 c.c.; light yellow; turbid	12	8	3	6	
				1½ h. a. b.	6 c.c.; yellow; greenish tinge; clear	10	11	6	5	
				2 h. a. b.	7 c.c.; yellow; clear; greenish tinge	12	13	3	4	
23	Mrs. A. L. M.	Biliary obstruction and fistula	HCl+; ac., 40	Feb. 19, 1918						
				Fasting	1 c.c.; yellow; turbid	15	5	Tr.	Tr.	
				½ h. a. b.	2 c.c.; yellow; turbid	20	5	1½	1	
				1 h. a. b.	3 c.c.; yellow; turbid	20	7	1½	Tr.	Pancreatic rennet +.
				1½ h. a. b.	6 c.c.; clear	70	16	2		
				2 h. a. b.	7 c.c.; yellow; turbid	−10	Tr.	Tr.	Tr.	Free acid present.
			GROUP V.							
24	Mr. J. M. M.	Achylia gastrica; probable cholelithiasis	HCl, 0; neutral	Feb. 23, 1918						
				Fasting	2 c.c.; yellowish green; slight turbidity	20	6	Tr.	1	
				½ h. a. b.	6 c.c.; brownish yellow; very slightly turbid	30	17	8	10	

				1 h. a. b.	1½ c.c.; yellow; very slightly turbid	20	5	2	1½	Urobiligen not present.
				1½ h. a. b.	2 c.c.; yellow; slightly turbid	40	11	Tr.	2	
				2 h. a. b.	2 c.c.; very slightly turbid	30	8	1	1	
				Mar. 24, 1918						
25	Mr. S. E.	Chronic myelitis; achylia gastrica	HCl, 0; ac., 0	Fasting	10 c.c.; yellow; turbid	35	12	1	5	
				½ h. a. b.	10 c.c.; yellow; greenish tinge; turbid	30	14	1	5	
				1 h. a. b.	½ c.c.; straw yellow; slightly turbid	20	9	3	6	
				1½ h. a. b.	1 c.c.; golden yellow; clear	25	11	2	4	
				Mar. 8, 1918						
26	Mr. A. A. C.	Carcinoma of the stomach	HCl, 0; ac., 25	Fasting	4½ c.c.; milky; turbid	50	8	2	Tr.	
				½ h. a. b.	6 c.c.; yellow; turbid; sediment	55	11	6	4	
				1 h. a. b.	6 c.c.; light yellow; turbid; greenish sediment	60	10	5	6	
				1½ h. a. b.	5 c.c.; greenish yellow and sediment	60	10	3	4	
				2 h. a. b.	1 c.c.; greenish yellow and sediment	60	9	Tr.	3	
				Group VI.						
				Jan. 12, 1918						
27	Mr. O. H.	Diabetes mellitus; thrombo-angiitis obliterans	.....	½ h. a. b.	Yellow; clear	20	6	12	2	
				1 h. a. b.	Yellow; clear	24	10	5	3	
				1½ h. a. b.	Yellow; clear	10	12	5	6	
				2 h. a. b.	Yellow; clear	20	6	1	2	
				Mar. 15, 1918						
28	Mr. C.	Thrombo-angiitis obliterans	.....	Fasting	4 c.c.; yellow; turbid	15	6	1	2	
				½ h. a. b.	½ c.c.; yellow; turbid	..	7	0	3	
				1 h. a. b.	5 c.c.; greenish-yellow; turbid	20	14	5	3	
				1½ h. a. b.	1 c.c.; yellow; greenish; slight turbidity	30	8	2	4	
				2 h. a. b.	¼ c.c.; yellow	..	8	0	3	

h. a. b. = hour(s) after bouillon.

TABLE OF CASES IN WHICH FRACTIONAL EXAMINATIONS OF THE DUODENAL CONTENTS WERE MADE—*continued.*

No.	Name.	Diagnosis.	Gastric contents.	Date and time.	Duodenal contents.					Remarks.
					Quantity and appearance.	Alkalinity.	Amylopsin.	Steapsin.	Trypsin.	
			GROUP VI—Continued							
29	Mr. S.	Thrombo-angiitis	.....	Jan. 31, 1918 Fasting	3 c.c.; watery; clear	..	0	0	0	
				1 h. a. b.	2 c.c.; yellowish	..	4	2	0	Rennet +.
				1 h. a. b.	½ c.c.; watery	N.	2	3	0	
				1½ h. a. b.	½ c.c.; watery	..	0	0	0	
30	Mr. B.	Thrombo-angiitis obliterans	.....	Jan. 29, 1918 ½ h. a. b.	6 c.c.; yellow; slightly turbid	25	5	1½	0	
				1 h. a. b.	3 c.c.; yellow; green; turbid	20	10	2	4	
				1½ h. a. b.	8 c.c.; gold; yellow; turbid	25	5	1	2	
				2 h. a. b.	3 c.c.; yellowish green; turbid	15	6	1	2	
31	Mr. M.	Thrombo-angiitis obliterans	.....	Jan. 30, 1918 Fasting	½ c.c.; yellow; clear	Alk	0	½	½	
				½ h. a. b.	3 c.c.; yellow; clear	10	0	Tr.	Tr.	
				1 h. a. b.	3 c.c.; yellow; clear	10	0	0	0	
				1½ h. a. b.	8 c.c.; yellow; clear	20	0	½	½	
				2 h. a. b.	3 c.c.; yellow; clear	−5	0	½	½	
32	Mr. K.	Thrombo-angiitis obliterans	.....	Mar. 27, 1918 Fasting	8 c.c.; whitish; turbid; no bile	5	6	8	1	
				½ h. a. b.	10 c.c.; yellow; greenish; turbid	55	11	5	6	
				1 h. a. b.	3 c.c.; light yellow; turbid	15	9	1	4	
				1½ h. a. b.	5 c.c.; whitish; turbid; no bile	15	9	5	1	
				2 h. a. b.	7 c.c.; whitish; turbid; no bile	20	7	2	2	

h. a. b. = hour(s) after bouillon.

The figures of the alkalinity fluctuated between 5 and 40 and were usually highest between one hour and one and a half hours after the bouillon test meal. The ferments, likewise, showed, in a general way, the same peculiarity, being strongest about that time.

Group IV comprises 4 cases of subacidity and 1 of cholelithiasis, with unknown gastric secretion. The degree of alkalinity fluctuated between 10 and 35; once it was 70 and once in the same patient, with the biliary fistula, it was found to be acid or −10. The strength of the ferments was usually highest between one and a half hours after the bouillon test meal.

Group V comprises 3 cases of achylia, 2 benign and 1 complicated with cancer of the stomach. The alkalinity fluctuates between 20 and 40 in the 2 benign cases and between 50 and 60 in the cancer case. The strength of the ferments is highest between half an hour and one hour after the bouillon test meal.

Group VI. Six cases of thrombo-angiitis obliterans, one of which was complicated with diabetes mellitus, were likewise examined. They were all patients of Dr. Willy Meyer and were treated by duodenal instillation of Ringer's solution. I am greatly indebted to Dr. Willy Meyer for permission to examine their pancreatic function. The alkalinity was, on an average, somewhat lower than normal, fluctuating between 10 and 24; once it was 5 and once 55.

In 3 of the 6 cases the ferment activity was at times greatly reduced (Cohen, Scherr, Metloff), the steapsin ferment showing the greatest variations.

Epicrisis. The grouping of the table was arranged according to gastric secretion in order to see whether the latter has any bearing on the alkalinity curve. *A priori*, one would expect a lowered alkalinity in cases of hyperchlorhydria and conversely an increased alkalinity in cases of subacidity. This seems to be true in a certain measure, but not constantly so. It seems there are other factors besides gastric secretion which play a part in regulating the degree of alkalinity of the duodenal contents. Chief among these are the pancreatic and duodenal juices and the bile. Each one of these is liable to have its own peculiarities and show alterations in disease.

It appeared worth while to look at the different types of alkalinity curves found, regardless of gastric juice or any disease present.

The accompanying types of alkalinity curves can be easily discerned.

Type 1 (Chart I). Decrease of alkalinity during the first half hour after the bouillon, then a steady increase.

Type 2 (Chart III). Increase of alkalinity between one-half and one hour after the bouillon, then slight decrease. Chart II belongs to Type 1, Chart IV belongs to Type 2.

Type 3 (Chart V). Increase of alkalinity during first half-hour after the bouillon, then slight decrease up to one hour, then again increase to one and a half hours, thereupon again a decrease.

Type 4 (Chart VI). There is first a steady increase of alkalinity up to one and a half hours after the bouillon test meal then an abrupt descent of the curve, so that at two hours after the bouillon the contents are acid instead of alkaline.

Of the three ferments each shows its individual peculiarities; the strength of one ferment cannot be gauged by that of the other. It is possible to ascertain the strength of each ferment at the different periods after the test meal and express it in the form of a curve. But each one (A. S. T.) has its own curve.

Object of Determining the Alkalinity. The pancreatic secretions act best in an alkaline medium. The reversion of the acid gastric contents into an alkaline mixture is an important function of the duodenum and its neighboring organs.

It can be easily imagined that in pathological conditions this harmonious work in having the right medium will be lacking. We may then have conditions in which the degree of alkalinity is too high, or again too low, *i. e.*, diminished alkalinity or slight acidity.

At What Time is it Best to Examine the Duodenal Contents? The fasting duodenal contents usually consist of some pancreatic secretion and bile, perhaps also duodenal secretion. The pancreatic juice at this time is generally weak in ferment activity and gastric contents are not admixed therein.

The duodenal contents one to one and a half hours after the bouillon test meal represent a chyle embracing the pancreatic juice at the height of activity, bile, duodenal secretion and an admixture of gastric chyme.

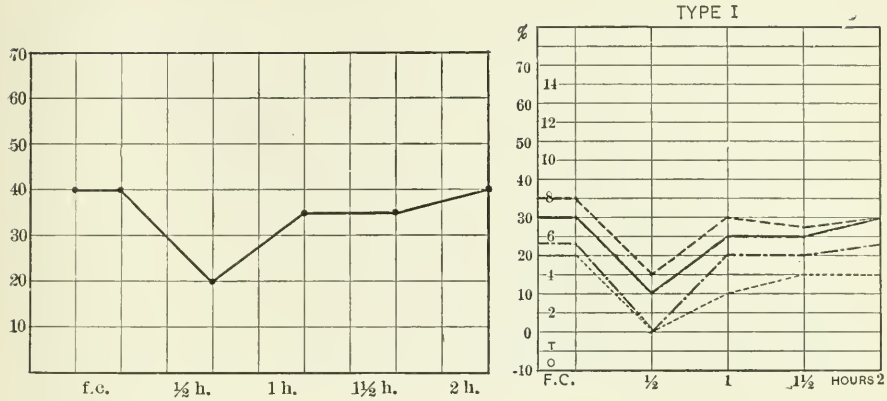

CHART I.—Case of Miss R. M. (No. 1). Alkalinity curve, Type I.

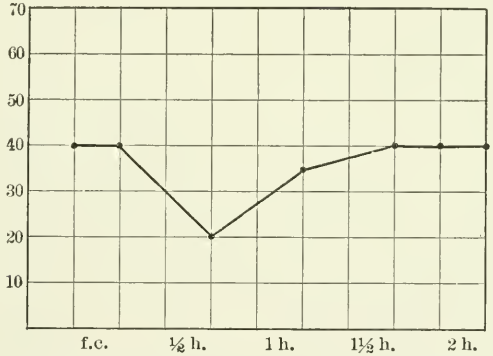

CHART II.—Case of Mrs. J. T. P. (No. 8). Alkalinity curve, Type I.

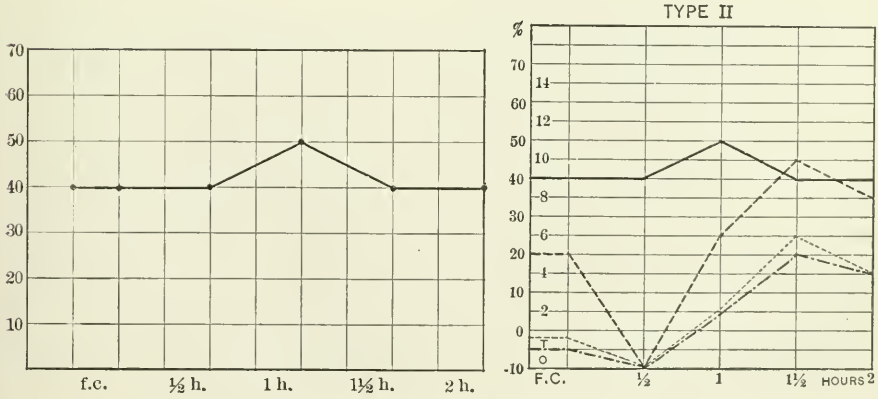

CHART III.—Case of Mr. J. M. W. (No. 5). Alkalinity curve, Type II.

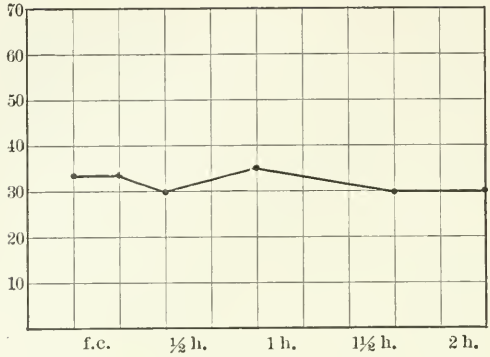

CHART IV.—Case of Mrs. J. D. (No. 19). Alkalinity curve, Type II.

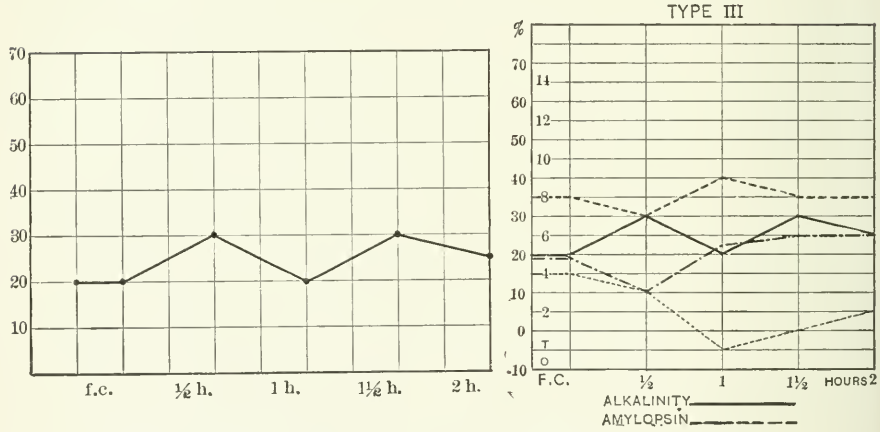

CHART V.—Case of Mrs. L. M. (No. 11). Alkalinity curve, Type III.

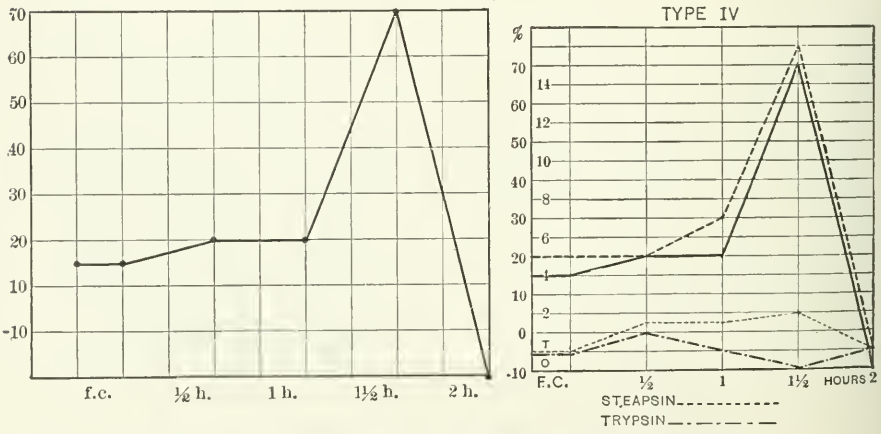

CHART VI.—Case of Mrs. A. L. M. (No. 23). Alkalinity curve, Type IV.

To facilitate the diagnosis of liver and gall-bladder lesions it appears that the examinations in the fasting state will give the best results. For here the investigation of the bile, in as pure a state as we can obtain it, will form the main object.

In pancreatic affections, also in all conditions in which the principal part of the digestive act should be investigated, it will be best to examine the duodenal contents one to one and a half hours after the test meal. The height of the pancreatic activity found at this moment and also the reversion of the admixed gastric chyme from an acid to an alkaline medium, which is a very important function of the duodenum, make this time best suited for the above purposes.

THE THYROID HORMONE AND ITS RELATION TO METABOLISM

By E. C. KENDALL, Ph.D.
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Much of the research work concerning the ductless glands has been from the viewpoint of relating some one gland to some particular portion or restricted function of the body. Thus, the pituitary has been associated with the growth of the bones and certain skeletal formations, the thyroid has been associated with the nerves, and some writers have satisfied themselves that the activity of certain ductless glands is explained by clinical syndromes, wherein only portions of the body show abnormalities. There have been relations suggested which were based on embryologic grounds. Organs and tissues derived from some common source have been supposed to be more or less related in function. Some of the most elaborate relationships of the ductless glands are based on histologic findings. The vast amount of research work that has been done with this object in view has indeed told us a great deal concerning the relationships of the ductless glands to certain bodily functions, but beyond this knowledge one cannot penetrate without new tools, and without applying quantitative determinations to the physiologic processes involved.

Before the chemical balance came into existence, the alchemist held sway over the theories of matter and the relationships existing between chemical substances. The phlogiston theory was unassailable on any ground other than quantitative analysis. From a survey of the literature today concerning the ductless glands we cannot boast of being very far out of the alchemist's age, and as yet very few investigators have approached the subject in a quantitative manner, with a realization of the actual problems existing.

For a complete analysis of the exact chemical reactions produced by this or that gland, nothing short of the actual isolation of the products in question can really solve the problem, and even after the chemical substances responsible for the activity of the various glands have been isolated, the interpretation of their physiologic functions requires not only the microscope, the kymograph and the chemical laboratory, but most of all the application of physics, chemistry, hydraulics and mechanics. Too much emphasis has been laid in the past on clinical and experimental conditions that are only partial expressions of a fundamental reaction which in almost every case has so far escaped detection. In the meantime these minor details have been stretched to the utmost in order that they may fit the theory of the supposed function of the gland in question.

Realizing that the function of the thyroid must be based on simple chemical reactions, and trusting in the probability that the substance producing these reactions would be stable enough to be separated, the isolation of the iodin compound occurring in the thyroid was begun by me eight years ago. During this investigation a very large amount of fresh thyroid glands has been used, and the work has been pushed in several directions, so that now not only has the isolation of the substance been accomplished but it has been analyzed, its empirical and structural formulæ have been determined, and its synthesis has been completed.* The physiologic action has been studied, and a large number of patients have been treated in the Mayo Clinic.

All this work has emphasized the necessity of viewing the function of any endocrine gland on the very broadest possible grounds. For example, in cretinism there is a certain characteristic expression of the face, the long bones do not grow normally, the skin is dry and scaly, the hair is scant and brittle, there is no ambition, and mental activity is very much below normal. Shall one then say that the thyroid controls the length of the long bones, the skin, the hair and the nerves? This is all true, but it does not deal with the actual function of the gland and the chemical processes involved. It is following only so far as the eye can see. In this instance quantitative

* Mr. Osterberg, working in our laboratory, succeeded in synthesizing a small amount of thyroxin in December, 1917. Further work is in progress.

studies have been directed to anatomic changes and not to physiologic processes. A change in the physiologic function is being interpreted in terms of the end-result produced by the change. One almost loses sight of the fact that the thyroid is just as vitally concerned in normal conditions. To the majority of those most interested the function of the thyroid does not mean a physiologic process based on chemical reactions, but the word brings to mind a disturbance defined in clinical terms.

According to the older view the active constituent of the thyroid functions within the gland itself. The blood passing through the gland is purified; before it enters the gland it is toxic to the organism, and after leaving the gland it is not toxic. Others have held that the location of the activity of the substance was in and through the nervous system, that through the nerves the various thyroid manifestations were brought about and that the secretion was carried from the gland to the nerves by the blood stream.

During the past ten years Plummer has been making a very detailed study of the function of the thyroid, and he has been led to believe that the location of the active constituent of the thyroid, when it functions, is within the cells not of any particular set of organs or portion of the body, but that it is a constituent of cellular life and activity. Plummer states that the active constituent of the thyroid determines the rate at which any particular cell can produce energy, that is, it establishes the quantum of energy which any cell can produce when it is stimulated either from within itself or from without, so that the thyroid is directly related to the production of energy within the body. He has shown that one-third of one milligram of the active constituent of the thyroid increases the basal metabolic rate 1 per cent. in an adult weighing approximately 150 pounds. Here we have not only a definition of the function of the thyroid, but it is expressed in mathematical terms with such exactness that the number of milligrams of the substance functioning within the entire body can be estimated. It is between 23 and 50 mg., that is, between one-third and two-thirds of one grain.

We are still confronted with the problem of the exact chemical reactions involved, but here again a great deal of light is thrown on the problem by the chemical constitution of the active constituent

of the thyroid. For reasons given hereinafter the substance has been named "Thyroxin."

When thyroxin is given to a myxedematous patient all the symptoms due to myxedema are promptly relieved. When it is given in too large amounts hyperthyroid symptoms are produced. This has been known now for more than three years, and on these grounds it has been stated that thyroxin is the active constituent of the thyroid. But the fact that a physiologic response is produced by the administration of a substance is not an explanation of the physiologic function of that substance, and it was not until a quantitative value was placed on thyroxin that the real physiologic processes involved could be demonstrated. It seems that one or the most important results of this work has been the furnishing of the material with which quantitative values could be determined.

The moment we know that in a myxedematous patient the administration of 10 mg. of thyroxin increases the basal metabolic rate 30 per cent., we have the key to the explanation of the relief of a very complex clinical syndrome. The edema is relieved. The sluggish mentality is relieved. The dry scaly skin becomes moist. The hair ceases to fall out and becomes soft. The voice that has been very slow, returns to its normal tone and character. The mentality which has been befogged becomes clear, and the individual expresses his normal personality. In short, every cell in the body responds with its own expression of activity. It seems impossible that all this can be done with a single crystalline substance, and because our knowledge has been limited as to just what and how much was going on, we have let visible changes lead away into theories that are narrow and which obscure rather than enlighten. But when we know that simultaneously with the clinical improvement the basal metabolic rate has been increased 30 per cent., it follows axiomatically, from laws of mechanics, hydraulics and physics, that very fundamental changes have occurred throughout the entire body. It has long been known that the thyroid influences basal metabolic rate in the body. It is a present-day conception that it is through metabolic processes that the thyroid produces its physiologic effect, but the scope of this action and the chemical processes involved have not been emphasized or established.

In order to explain the action of thyroxin, when 10 mg. of the substance increases the metabolic rate 30 per cent. as Plummer puts it, it would take a discussion as broad as biology itself. This aspect of the question must receive greater attention in order to bring out the physiologic processes involved in the function of the thyroid, and with it, the other ductless glands. The scope of the problem is so broad that several investigators viewing it from entirely different standpoints can each obtain results satisfactorily conforming to their conclusions, but no one of which forms a fundamental physiologic process. For instance, investigating the question of resistance to infection, the removal of the thyroid establishes the fact that in thyroidless animals infection is much more prevalent. This is of interest to the bacteriologist, serologist, immunologist, etc. The fact that the growth of bones is retarded is an entirely different phase of the subject, and so, a long list of investigations concerning the thyroid which have been carried on with positive results leading to various conclusions concerning its activity, could be cited.

Until it was shown that the confusing clinical syndrome found in myxedema could be entirely relieved by a single substance, the problem as to how many active constituents occurred in the thyroid could not be settled. In fact, the fundamental reaction underlying all expressions of thyroid activity could not be made as long as clinical symptoms alone were used as a criterion of physiologic activity. But, establishing the relation of thyroxin to the basal rate of metabolism in mathematical exactness furnishes the first clew to the physiologic processes involved, and it is evident that physiologic response to an injection of thyroxin is found in a summation of the activity of all the cells in the body. If anyone chooses to investigate any one particular process he will find that process altered, for a change in metabolic rate is accompanied by fundamental changes in every aspect of the reactions going on within the body. This is where the application of physics, mechanics, hydraulics and chemistry must be made in order to understand, not only the changes produced by the administration of thyroxin, but what the effect of a second factor would be.

The injection of adrenalin into an animal with a normal basal metalbolic rate will necessarily be different from the injection of

adrenalin into an animal with a metabolic rate 30 per cent. above normal, if viewed purely from a consideration of the physics involved. As Plummer has pointed out, it is possible to explain the supposed relation between thyroid and adrenalin on grounds involving the rate of flow of the blood, entirely apart from any other action.

When it comes to establishing relations between the other ductless glands and the thyroid, progress can only be made when the various activities of the glands are viewed in as broad an aspect as Plummer has suggested for the action of thyroxin. Disturbances of the pituitary lead to changes in basal metabolic rate which are marked but are less than those found in thyroid disturbances. Changes in the pancreas and what we know of the adrenal also lead to changes which are smaller than that produced by thyroxin. We can at least tentatively assign to the thyroid the supplying of an agent which is of fundamental importance in the production of energy. This can be carried one step further in a chemical sense, and we may assume that thyroxin is involved in the production of carbon dioxide. The other ductless glands then assume positions of secondary importance to the thyroid, in carrying out these chemical reactions, and may be assigned the role of preparing the various metabolites for their final action with thyroxin. No definite hypothesis can at this time be given beyond the fact that the various clinical syndromes produced by hyper- or hypo-action of the various glands, are syndromes resulting from the effects of these substances throughout all the cells of the body, through their action in maintaining the rate of energy production going on within the cells.

It is perfectly possible to explain the apparent selective action of various internal secretions to restricted portion of the body on these grounds, and in fact selective action vanishes when the action of the gland is placed on this broader basis.

Beside the action suggested for certain of the ductless glands of preparing metabolites for their final interaction with thyroxin with the production of energy, we must also assign to some agents within the body the task of taking care of bi-products and of elaborating other substances. Nitrogen compounds include toxic substances among their number. For the proper elaboration of these compounds, which assume fundamental importance in normal physi-

ology, some very substantial mechanism must exist. That certain of the ductless glands should be given the power to affect the rate at which the body can prepare and care for nitrogenous compounds seems highly probable, and of late the parathyroid assumes great importance as one of the glands thus involved. That others of the glands are also concerned also seems to be indicated.

It was therefore of great interest to determine the chemical nature of this iodin containing compound which occurs in the thyroid and is so fundamentally involved in normal physiology. Analysis has shown that it contains an indol group with the iodins undoubtedly attached to the benzene ring, and that on the carbon atom adjacent to the imino group of the indol ring there is an oxygen atom (Fig. 1).

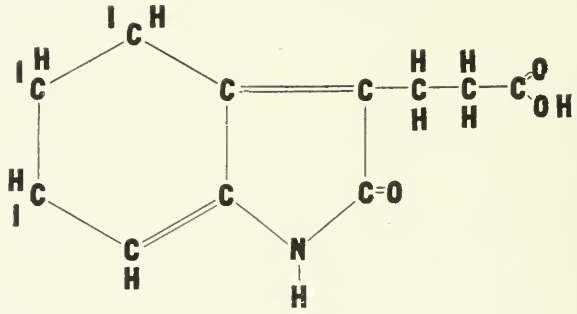

FIG. 1.—The structural formula of the active constituent of the thyroid.

For reasons given hereinafter, it appeared desirable to emphasize the presence of the oxy-indol nucleus and it appeared equally desirable not to emphasize the presence of iodin. The substance was therefore named "Thyro-oxy-indol," which has been shortened to "thyroxin" for every-day reference to the substance. At first we attempted to show that the activity of thyroxin was due to the oxygen condensing with the amino group of an amino acid and the carboxyl group of the amino acid reacting with the imino group of thyroxin. It has been shown, however, that this does not occur; but that the physiologic activity of the substance is produced by the CO-NH groups has been demonstrated as follows:

The injection of pure thyroxin is followed by a very definite and marked physiologic response. When the hydrogen on the imino

has been replaced with acetyl the substance loses its physiologic activity and the injection of the substance is without demonstrable effect. Investigation of the acetyl showed that, in alkaline solution, the indol form of the compound no longer exists, but that there is hydrolysis of the CO and NH groups resulting in the opening of the ring and the formation of COOH and NH_2 (Fig. 2). Further investigation showed that the thyroxin behaves in this same way, and that it exists within the body, not in the closed ring form such as is present in indol, but in the form COOH NH_2. The ability of the indol ring to thus open, furnishes the first concrete conception of how the substance behaves chemically within the body. The fact that both thyroxin and the acetyl derivative exists in open form,

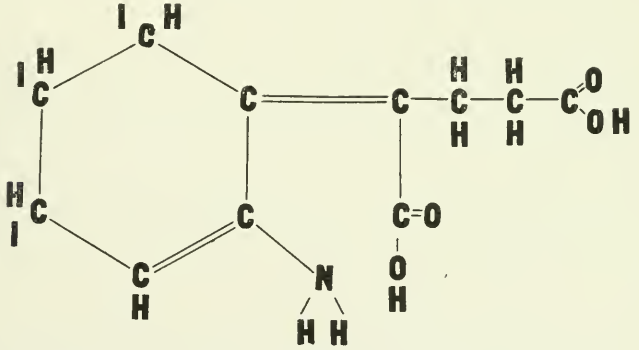

Fig. 2.—The open ring form of thyroxin as it exists in the body.

suggests that the reason for the inactivity of the acetyl is because of interference with the chemical reaction associated with the NH_2 group of thyroxin. One is at once struck with the fact that the open and closed forms of thyroxin bear to each other the same relation as does creatin to creatinin, and the same relation exists between amino acids and the form in which amino acids are united in protein. Establishing these active groups emphasizes the importance of the chemical nucleus CO NH and COOH NH_2 within the body, which appears to be a necessary structure for the carrying out of chemical changes leading to the production of energy.

Patients with complete atrophy of the thyroid have basal metabolic rates approximately 40 per cent. below normal. It has been

shown that administration of thyroxin alone can bring back and maintain the normal metabolic rate in such patients. But in complete atrophy of the thyroid, the complete or nearly complete absence of thyroxin may be assumed. The question arises as to what maintains energy output from 100 per cent. below normal, which would be death, up to 40 per cent. below normal, the point to which basal metabolism sinks in the absence of thyroxin. May it not be the other chemical substances in the body possessing the same grouping that occurs in thyroxin? These are amino acids and proteins, creatin and creatinin, and a few other less well-known compounds. It seems probable that on the administration of thyroxin a reaction which has been carried on within the body by other compounds is merely increased in rate, but that there is no difference or disturbance of the reactions that have been going on.

In regard to the relation of iodin to the activity of thyroxin, the presence of iodin in the compound must exert some influence, and it seems not improbable that the presence of iodin renders the active groups more reactive. In the absence of iodin it would take a greater working pressure to bring about its reaction. The substitution of the iodin by hydrogen or chlorine or bromine would undoubtedly be followed by an alteration in the degree of reactivity of the substance, but its gross chemical nature and properties would not be altered thereby. That the iodin breaks off from the molecule and is used as iodin *per se* for any purpose, seems absolutely impossible because Plummer has shown that this substance functions for as long as from fifteen to twenty-one days after being administered, and that it acts as a true catalyst, being used over and over, hour after hour, without destruction except at a very low rate. It is finally removed from the body either by actual destruction, or by slow loss in an undestroyed form. Our knowledge of other catalytic agents shows that poisoning of catalysts is common if not universal, so that its slow destruction is to be expected.

The exact chemical reactions involved when this substance functions are still unknown, but that the substance possesses the formula as shown above is established by the ultimate chemical analysis of its derivatives. That the active groups present in thyroxin are a necessary mechanism for the production of energy within the body

seems highly probable, and it is of great interest and significance that there exists a close analogy between this substance, whose exact effect on metabolism we know, and other substances, creatin, creatinin, amino acids and proteins, which are also intimately associated with reactions occurring within the animal organism. Are these substances also concerned in the maintenance of the basal metabolic rate?

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THE ROLE OF THE VASOMOTOR RESPONSE IN THE CARDIAC AND RENAL DECOMPENSATION OF HYPERTENSIVE CARDIO-VASCULAR-RENAL DISEASE

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It is, we believe, conceded by physiologists that the five factors concerned in the maintenance of normal circulation of the blood and blood-pressure are:

1. The propelling force of the heart.
2. The elasticity of the arterial walls.
3. The peripheral resistance.
4. The viscosity of the blood.
5. The volume of circulating blood.

1. The heart's propelling force depends, of course, mainly on the integrity of the cardiac muscles.

2. The arterial tree having been distended by the ventricular contraction to receive with lessened resistance the volume of blood discharged from the heart, recoils on itself by virtue of the elasticity of its coats and thereby greatly assists in conjunction with the closure of the semilunar valves in the forward movement of the blood column during diastole and in the establishment in the capillaries of a steady blood stream to supplant the intermittent spurt of the larger arteries, so that the assistance of the elasticity of the arterial wall to the action of the heart is thus a twofold and important one, namely, to lessen the resistance ahead of the contracting organ in systole and to continue the propelling force of the pump during the period

of cardiac repose, when, according to Howell,[1] as much blood is forced into the capillaries as during the systole.

3. The peripheral resistance is maintained through the vasomotor system of nerves, whereby, through a beautiful nervous adjustment, the arterial tree is in health maintained at just the proper caliber by the action of the vasoconstrictor or pressor set of vasomotor fibers with its governing center in the cerebrospinal system and with subsidiary stations, so to speak, in the sympathetic ganglia. Through constant stimuli of these vasomotor constrictor nerves distributed to the muscular coats of the arteries the normal tonus of the bloodvessels, with normal blood-pressure, results. But should the action of these vasoconstrictor nerves become excessive from whatever cause, then will come into play another set of fibers, namely, the vasodilators, or depressor nerves, the terminals of which, distributed as they also are to the walls of the arteries, being stimulated by the excessive strain on the vessel walls of the abnormal vasoconstriction and excessive blood-pressure, send centripetal impulses which reflexly either inhibit the action of the vasoconstrictors or else overpower them with stronger vasodilator impulses. Though apparently thus able to control under some conditions the action of the vasoconstrictor fibers, this vasodilator system of nerves in certain pathological conditions appears unequal to the control of excessive vasoconstriction and hypertension.

This third factor, or the peripheral resistance, depends therefore mainly on the caliber of the arterial tree as maintained by the vasomotor nerves whereby also, associated with ventricular contraction, is determined blood-pressure; and upon such mutual action between the driving power of the heart and the arterial caliber are based the following laws of Marey:[2]

1. "Whatever increases or diminishes the force with which the blood is driven from the heart toward the periphery will cause the velocity of the blood and the pressure in the arteries to vary in the same sense." That is, other conditions being equal, the greater the driving force of the heart the greater will be the velocity of the blood flow and the higher the blood-pressure, and *vice versa*.

[1] 1915, p. 314.

[2] La Circulation du Sang, Paris, 1881, p. 321.

2. "Whatever increases or diminishes the resistance offered to the blood in passing from the arteries to the veins will cause the velocity and arterial pressure to vary in an adverse sense as regards each other." The greater therefore the peripheral resistance, other conditions also being equal, the less will be the velocity of the blood but the higher the blood-pressure, and *vice versa*. This intimate interrelation between the pump action of the heart and the maintenance of the proper caliber of the arterial tree, through the vasomotor system, cannot fail therefore to impress us with the great importance of these two factors in the circulation of the blood in health.

According to Adami[1] and Nichols: The muscular arterioles then as guarding the gateway into the capillaries are, with the heart, the main agents in maintaining the circulation, and, as a rule, through the marvellously developed vasomotor apparatus they act in absolute harmony with the heart on the one hand and with the needs of the individual organs on the other.

The remaining two factors in the circulation of the blood in health, namely, the volume of the blood within the vessels and its viscosity, are practically very little concerned in the circulatory disturbances of disease and therefore considered as almost negligible in this study.

Hypertension is held today to be due to stimulation of the vasoconstrictor fibers supplying mainly the arterioles resulting in their vasoconstriction and consequent increase in peripheral resistance and rise in blood-pressure. The cause of this vasoconstriction is assumed to be the presence in the blood of certain substances having the power to stimulate the vasoconstrictor apparatus.

As Lauder Brunton says, this condition is demonstrable in migraine, where the blood-pressure is found raised through vasoconstriction of the arteries or arterioles, and, as a matter of fact, the superficial vessels as the temporals can actually be seen firm, contracted and whipcord-like—a condition which is generally conceded to be due to errors in diet resulting in imperfect metabolism, developing poisons which produce vasoconstriction through stimulation of vasoconstrictor system of nerves.

[1] Principles of Pathology, vol. ii, 2d edition.

To quote Adami again: "Artificial contraction, and particularly a generalized arterial contraction, is the primary cause of heightened blood-pressure. The persistent rise of blood-pressure, or the condition termed by Sir Clifford Allbutt as 'hyperpiesis,' is the commonest precursor of arteriosclerosis." The name given thirty years ago by Gull and Sutton of arteriocapillary sclerosis is quite defensible in that a fibrosis of the arterioles characterizes the most important group of cases and has a clear relationship to the development of the changes in the larger arteries.

There are then two main causes of arteriosclerosis: (1) Increased strain thrown on the arterial wall by heightened blood-pressure, and (2) a weakened state of the wall either from congenital causes or disease. Hence, there may be arteriosclerosis with high and with low blood-pressure. If the pressure be normal and the walls weakened the results are of the same order as when the pressure is heightened but the walls of normal resisting power. It is not the hypertension alone which causes arteriosclerosis, but it is the ratio between the resisting power of the vessel wall and the pressure to which it is subjected from within, and it follows as a natural corollary that the arterial tree is not equally resistant in all its parts; hence, in some subjects the large vessels are mainly affected, in others the small ones and in still others the changes are universal.

Calcification of arteries of the second and third degree may be extreme, becoming like rigid tubes. In them we have demonstrated most strikingly the thinning and giving away of the media beneath the overlying great thickening of the intima. In one important series of cases we have stimuli acting on the media of the smaller arteries causing tonic contraction or hypertonus with resulting hypertension, the strain of which causes atrophy and degeneration of the media with a compensatory fibrosis of intima. In the other class of cases we have the same pathological conditions resulting from weakness, either inherited or acquired, of the median coat, but without any preceding hypertension.

Thus do Adami and Nichols present the subject, and it would seem to us that we may add that in the first class of cases we may have a fixation so to speak of the arterial tree in a condition of vasoconstriction either from the sclerotic process or from persistent

hypertonic contraction, giving us the refractory vasomotor response and irreducible hypertension; while in the second we have fixation of the arterial tree which has not been preceded by vasoconstriction and with therefore no element of hypertension. Arteriosclerosis therefore may be divided from the standpoint of causation into

1. Senile or involutionary, which is not accompanied by hypertension.

2. Luetic, which is not, *per se*, hypertensive.

3. Hyperpiesis, which, resulting from vasoconstriction primarily, is therefore practically always accompanied by increased blood-pressure.

The greater the degree of these pathological changes the greater the loss of the function of the elastic and muscular coats of the vessels and of the vasomotor response until their more or less obliteration, when the walls of the arteries and the arterioles become absolutely rigid and fixed from calcareous degeneration.

Some have argued that such a fixed condition in the arteries and capillaries could never become possible because of its interference with the vasomotor control of the metabolic processes. The answer to which is that with the pathologists granting calcareous degeneration of the arterioles and capillaries it is inconceivable how a rigid fixed calcareous vessel wall can to any extent retain its vasomotor response. Then, too, we do frequently have a definite disturbance of metabolism in arteriosclerotics resulting in progressive loss of weight, which cannot be reasonably explained on any other basis than that of deficient blood supply to the tissues.

Howell does not deny such a possible disturbance in metabolism as just above stated, but avers that such a condition has not been as yet scientifically demonstrated.

Accordingly to Janeway:[1]

1. "Hypertension may arise through purely quantitative reduction of kidney substances below the factor of safety—it is difficult to consider this as other than a muscular hypertonus due to retained poisons of some kind. Its clinical paradigm is the hypertension accompanying bilateral ureteral obstruction or in the unfortunate surgical removal of the only functionating kidney. Possibly it is

[1] Blood-pressure, its Clinical Application, 1916.

one factor which helps to produce hypertension in the contracted kidney.

2. Hypertension may arise in connection with unknown intoxication which causes disturbances of the central nervous system and which we call uremia. This intoxication is not one of retention in the strict sense of the word, although it is most commonly present in those cases of advanced nephritis which manifest marked nitrogen retention—clinically it is associated with severe acute nephritis, sometimes at its very onset, besides the subacute and chronic affections of the kidney.

3. Hypertension may arise in primary irritability of the vasoconstricting mechanism, from unknown extrarenal causes, which leads eventually to arteriosclerosis. In this type the disease in the kidney is the sequence not the cause of the generalized vascular lesion. When it progresses to a condition of extreme atrophy, resulting in true primary contracted kidney, a renal element may be added to the existing hypertension. In some cases arteriosclerosis may spread peripherally and produce a similar form of disease. In these forms of primary vascular disease it is probable that eventually widespread narrowing of the arterial stream bed in some cases produces a permanent organic increase in peripheral resistance."

It has generally been assumed in the past that hypertension was of renal origin. That by loss of functionating tissue in these organs, toxic products accumulated in the blood which produced vasoconstriction, so that thereby, through raising of blood-pressure, more blood might be driven into the kidneys in a given time and their disturbed function in this way maintained. In other words, that the hypertension was a compensatory conservative condition and that therefore it was dangerous to try to lower blood-pressure because the result would be a falling urine supply and uremia.

Lawrence,[1] however, found that clinical reports were by no means unanimous in declaring hypertension to be conservative and protective, and quotes numerous investigators to the effect that a lowering of pressure was coincident with improvement. Experimental studies also show that (*a*) decreased renal tissue is not the cause

[1] The Relation of Hypertension to Urinary Secretion, Am. Jour. Med. Sc., September, 1912, 330.

of hypertension; (*b*) that the latter does not cause an increased blood flow through the kidney; (*c*) that hypertension is not accountable for the polyuria. There undoubtedly also is a large group of cases, as stated by Janeway, in which the hypertension and arteriosclerosis are the primary conditions, the sclerotic process extending later to the renal arteries developing the arteriosclerotic kidney as a secondary condition. It is with this and the other extrarenal groups that our study is especially concerned.

Janeway[1] in 458 patients with systolic pressure of 160 or over found 116 with neither albumin nor casts and 91 with albumin, but without casts or casts without albumin, and though it may be contended that there may be nephritis without evidence in the urine, still pathologists hold that normal kidneys are found in cases of hypertension, and it has been demonstrated that while renal disease and hypertension are frequently associated, the kidney changes cannot be held as the sole cause of hypertension.

While therefore there may be certain cases in which the disease originating mainly in the kidney, there may result from deficient kidney function the accumulation of certain substances in the blood which, exerting a vasoconstrictor influence, may cause hypertension, yet such hypertension under those conditions may be considered simply as a necessary result of the kidney decompensation and therefore not as compensatory or conservative, and furthermore, as being capable of being lowered where vasomotor response is not lost without necessarily any increase in the renal decompensation. And, again, the same agencies which produce the hypertension and the arteriosclerosis may cause also the nephritis. In fact, it is more generally considered that these substances in the blood causing vasoconstriction, and called therefore "pressor substances," result most probably from faulty metabolism in the protein group for protein cleavage going through the successive stages of albuminose peptone and amino-acids, the latter being absorbed to repair tissue, catabolism and any portion above these needs adds just so much more waste for kidney elimination resulting in more or less nitrogen retention. Excessive protein diet also results in undigested proteins being reduced in the large bowel by putrefactive bacteria and the

[1] Am. Jour. Med. Sc., 1913, cxiv, 625–656.

formation of simpler products by digestive enzymes which are highly toxic, and which, not being destroyed by the detoxicating influence of the liver, enter the general circulation and become so-called pressor substances. The majority of cases of hypertension show an excess of non-protein blood nitrogen in the blood.

More recently Voegtlin and Macht succeeded in isolating from the blood serum a crystalline presser substance whose pharmacological action is different from epinephrin and from any other body heretofore obtained from the blood. It produces marked cardiac stimulation and a prolonged vasoconstrictor effect. They considered it related to cholesterin on the one hand and the adrenal cortex on the other.

Foster, in 1915, reported isolation of a crystalline substance from blood of uremic patients which raised blood-pressure, but the true nature of neither of the above bodies is as yet definitely known. Perhaps the next best accepted causes of hypertension are the various focal infections, as in the teeth, the accessory sinuses to the nose and elsewhere in the body.

Students in endocrinology have advanced the hormonic theory. In chronic cyanosis due to failing heart we have hypertension due to stimulation of vasoconstrictors from overloading of blood with CO_2. In some cases of polycythemia we have, without as yet adequate explanation, high blood-pressure.

We divide the effects on hypertension as follows: (1) on the arteries, (2) on the heart, (3) on the kidney.

The effect of hypertension on the arteries is:

1. Through the vasoconstriction to interfere with the dilatation of the arterial tree in the receipt of the cardiac systolic output and to limit the elastic recoil of the arterial wall in diastole and the consequent carrying forward of the blood column.

All the above disturbances in the vasomotor response of the arterial tree become progressively increased as sclerosis and calcareous degeneration follow on the heels of the strain on the vessel wall of hypertension.

The effect of narrowing of lumen of the arterial tree, whether from simple vasoconstriction or fixation, tends to greatly increase peripheral resistance.

2. These effects of hypertension on the arteries involve the cardiac function as follows:

The heart is deprived of the great assistance rendered the organ by the elastic dilatation and increase of the caliber of the arterial tree for the receipt of the systolic cardiac output, as also through the removal of the force exercised during the cardiac repose by the elastic recoil of the vessel walls—so that the strain on the heart is greater both during systole and diastole.

The strain increases as the arterial disease progresses from vasoconstriction through sclerosis to calcareous degeneration of vessel walls.

The work of the heart is greatly augmented by the increased peripheral resistance consequent on vasoconstriction sclerosis and calcareous degeneration of the arterial tree.

The cardiac compensation established to meet this tremendous increase in work through hypertrophy, especially of left side of the heart, reaches a point finally as in valvular disease when muscular fatigue results and when dilatation begins to predominate over hypertrophy and finally there is depicted the scene of decompensated cardiac disease with all its dire consequences on to the fatal termination.

This break in cardiac decompensation may be hastened by sclerosis or calcareous degeneration of the coronary arteries leading to chronic myocarditis, myocardial degeneration, or cardiosclerosis.

3. This same arterial vasoconstriction, sclerosis and calcareous degeneration may extend into the renal arteries resulting in degenerative changes in the renal parenchyma and secondary fibrosis in the interstitial tissue, resulting finally in the typical sclerotic kidney.

Cardiac decompensation develops the kidney of stasis which may increase the already existing renal decompensation.

Renal decompensation developing in the sclerotic or kidney of stasis tends to increase the toxic substances in the blood establishing a tendency toward a vicious circle.

We have seen in thus reviewing the status of the question of hypertension today that it has been considered by some clinicians as a compensatory conservative condition that must not be lowered for fear of precipitating thereby either renal or cardiac decompensa-

tion, and even those who have doubted this doctrine because of observing cases from time to time where improvement followed in both cardiac and renal decompensation with fall in blood-pressure, still have as yet offered no explanation for their doubts. It is our hope to carry the solution of this question perhaps a step further in an effort to show that, in hypertensive cardiovascular renal disease, first, when the vasomotor response is retained hypertension is never conservative and is only necessary when the vasomotor response is refractory or lost and to be ultimately destructive when blood-pressure is found permanently irreducible. These statements will be made more clear by the following classification of cardio-vascular renal disease which we also offer merely as a working hypothesis which, however, we hope and feel to be able to establish as true through future study.

The cases are first divided into:

A. Those with vasomotor response retained and therefore with mobile arterial tree.

B. Those with vasomotor response lost or refractory arterial tree.

Group B is further divided into:

1. Vasomotor response refractory temporarily or permanently through presence in blood of irremovable pressor substances.

2. Vasomotor response permanently refractory from sclerosis or calcareous degeneration of arterial wall.

And from these main divisions are derived the groups represented in the charts which embrace 53 cases studied under the following conditions:

(*a*) These patients were selected from the general admissions to the Internal Medical Service and Out-patient Department of Barnes Hospital and a few from our own private clientèle who had at least one systolic reading of 160 mm. of Hg. or more and in whom blood-pressure records had been kept.

(*b*) The Faught mercury instrument was used up to July, 1917, and after that the tycose spring instrument, checked up by the mercury apparatus, was employed. The auscultatory method was resorted to in all cases.

(*c*) The physical examinations were in all the hospital cases checked up by Drs. Dock and Robinson and also Dr. Andrews, the

house physician, the interns and ourselves and all doubtful points were studied with the aid of the *x*-ray and of the electrocardiogram. The diagnosis was confirmed by necropsy in a few of the cases.

(*d*) The presence of arterial sclerosis was determined by careful examination in the majority of the cases of radial, brachial, temporal, femoral, posterior, tibial and dorsalis pedis arteries and in some cases also of the retinal vessels; and in a few cases through post-mortem findings.

(*e*) None of these cases were observed from our standpoint by the other members of the Internal Medical Staff, so that the observations made by them had the greatly added weight of being entirely unbiased.

After consideration of any possible focal infection, the treatment of this group of cases consisted mainly:

1. In the hospital group of absolute rest, whereby were limited not only the number of heart-beats but also the catabolic processes.

2. The diet which generally was that designated in the service as low nephritic, in which the protein intake was greatly limited, some where on largely a milk diet while others were placed on a strict Karrel regimé.

3. Elimination with the object of removing the so-called pressor substances from the blood (*a*) through the bowel, (*b*) through the skin, and (*c*) through the kidney.

(*a*) Through the Bowel: Resort was not only had to purging the intestinal tract through the salines but to also clear out thoroughly the portal circuit through the administration of the so-called cholagogue remedies, as calomel, blue mass, compound cathartic pills, etc., whereby to prevent the toxic products of protein cleavage reaching the liver through the portal vein, and which, escaping the detoxicating influence of the hepatic function, to gain access to the blood.

(*b*) Through the Skin: The daily toilet of the skin to increase its activity and with uremic tendencies, sweat baths, etc.

(*c*) Through the Kidney: When not contra-indicated by edema, systematic water-drinking and, where sufficient kidney parenchyma remained, of such diuretics as diuretin, agurin and theosin.

4. The vasodilator group of remedies were only used to meet critical emergencies.

5. An assayed tincture of digitalis was used in the cases of cardiac decompensation, and with the presence of auricular fibrillation the digitalis was administered in massive doses.

6. A minimum amount of opium was ordered, and, when possible, codein was preferred to morphin because of its interfering less with the urine output.

7. The serous sacs were kept emptied of accumulations, not only for the relief of dyspnea, but also because of the interference of pleural exudates with the respiratory assistance to the circulation.

We feel as yet not justified in drawing any definite conclusions from our work, so that the following tentative impressions only are offered:

1. Hypertension is never conservative for either heart or kidneys, but always destructive sooner or later to these organs.

2. An effort should always be made to reduce it; if successful the walls of the arterial tree and the heart and kidney compensation will be conserved and their decompensation improved or relieved. If unsuccessful no harm will have been done to either heart or kidneys or arteries.

3. Individuals at about middle life should report to their physicians as they do to their dentist, so that hypertension may be detected and controlled before becoming refractory and thereby preventing all the dire aftermath in heart and kidneys and blood-vessels tending toward a fatal termination.

4. Even after hypertension has become apparently refractory it may yet prove controllable later when not at first, and even if permanently uncontrollable, if heart compensation has yet not been disturbed, much can be done to conserve cardiac compensation, and after its failure it may be for a time at least restored.

In conclusion, we desire to express our grateful appreciation of the kindly interest of Drs. Dock and Robinson, who have made our study possible by placing at our disposal the rich clinical material of the wards and the Out-patient Department of the Barnes Hospital, and to Dr. Andrews, house physician, and the intern staff for valuable coöperation.

We wish to add again that this report is purely a preliminary one, which we hope to be able to develop not only through more complete study of future cases along the lines herein sketched but also through investigation of new avenues so far disclosed to us.

TABLE I.—VASOMOTOR RESPONSE RETAINED. BLOOD-PRESSURE LOWERED BY VASODILATION. CARDIAC AND RENAL COMPENSATION CONSERVED.

Case No.	Sex.	Race.	Age.	Symptoms.	O.C.D.	Vessels.	Blood-pressure.		P.S.P.		Urine.		N.P.N.		Diagnosis.	Result.	Days Observed.
							Entrance.	Discharge.	Ent.	Dis.	Entrance.	Discharge.	Ent.	Dis.			
3798	F	W	29	Compensation good	3–12	Not thickened	175–90	130–70	73	..	Alb. 0 Casts 0	Alb. 0 Casts 0	33	..	Arteriosclerosis	Not disturbed	22
2957	F	W	64	Compensation good	3–15	Thickened	210–90	143–72	68	..	Alb. + Casts 0	Alb. 0 Casts 0	16	..	Arteriosclerosis	Not disturbed	92
2476	M	W	62	Compensation good	3–14	Thickened	159–92	145–85	..	..	.....	.....	..	..	Arteriosclerosis; diabetes	Not disturbed	14
2611	F	C	42	Compensation good	2–9	Thickened	195–110	120–90	..	..	.....	.....	..	..	Arteriosclerosis	Not disturbed	28
3059	M	C	59	Compensation good	3–10	Thickened	185–105	155–75	..	..	.....	.....	..	..	Arteriosclerosis	Cerebral hemorrhage	11
15552	F	W	60	Compensation good	2–10	Thickened	235–130	210–110	60	..	Alb. + Casts 0	Alb. + Casts 0	29	..	Arteriosclerosis; nephritis, chronic	Not disturbed	23
34809	M	W	50	Compensation good	3–11	Thickened	190–110	120–100	..	..	Alb. + Casts +	Alb. 0 Casts 0	..	..	Arteriosclerosis; nephritis, chronic	Not disturbed	132
36555	F	W	39	Compensation good	3–15	Not thickened	200–100	140–85	50	..	Alb. + Casts +	Alb. 0 Casts 0	38	..	Arteriosclerosis; nephritis, chronic lues	Not disturbed	210
35399	F	C	51	Compensation good	4–10	Thickened	230–150	185–115	..	..	.....	.....	..	..	Arteriosclerosis	Not disturbed	14
35746	F	W	49	Compensation good	2–9	Thickened	200–85	148–70	..	..	.....	.....	..	..	Mitral insufficiency	Not disturbed	115
38863	M	W	46	Slight dyspnea	3–11	Thickened	188–105	177–92	..	..	.....	.....	..	..	Myocarditis, chronic	Not disturbed	150
36588	F	W	43	.....	....	Thickened	190–105	140–90	..	..	.....	.....	..	..	.....	Not disturbed	60

O. C. D. is outline of cardiac dulness. P. S. P. is phenolsulphonephthalein test. N. P. N. is non-protein nitrogen. This table clearly shows that blood-pressure can be definitely lowered through vasodilatation without the slightest disturbance either in cardiac or renal compensation, but with what must prove to be actual conservation of said cardiac and renal compensation as also of walls of the arterial tree.

TABLE II.—VASOMOTOR RESPONSE RETAINED. BLOOD-PRESSURE LOWERED BY VASODILATION. CARDIAC AND RENAL DECOMPENSATION IMPROVED.

Case No.	Sex.	Race.	Age.	Symptoms.	O.C.D.	Vessels.	Blood-pressure.		P.S.P.		Urine.		N.P.N.		Diagnosis.	Result.	Days observed.
							Entrance.	Discharge.	Ent.	Dis.	Entrance.	Discharge.	Ent.	Dis.			
2484	F	W	44	Dyspnea, edema	3–20	Thickened	230–115	185–85	45	50	Alb. 0 Casts 0	Alb. 0 Casts 0	..	..	Auricular fibrillation; nephritis, chronic	Compensation restored	28
3877	F	W	45	Dyspnea, edema	3–10	Thickened	222–114	156–86	..	..	Alb. ++ Casts ++	Alb. + Casts +	13	..	Myocarditis, chronic; nephritis, chronic	Much improved	26
2579	M	W	64	Dyspnea, edema	5–14	Thickened	165–110	115–75	15	58	Alb. ++ Casts ++	Alb. + Casts 0	46	..	Auricular fibrillation; nephritis, chronic	Much improved	36
4148	F	W	60	Dyspnea, edema	2–9	Thickened	183–95	133–83	50	..	Alb. + Casts 0	Alb. 0 Casts 0	35	35	Auricular fibrillation; nephritis, chronic	Much improved	14
2839	M	W	39	Dyspnea, edema	2–9	Thickened	160–100	90–50	42	44	Alb. + Casts 0	Alb. 0 Casts 0	26	..	Auricular fibrillation; nephritis, chronic	Much improved	22
4789	F	C	41	Dyspnea, edema	2–9	Thickened	230–175	185–135	7	20	Alb. ++ Casts ++	Alb. + Casts 0	44	..	Auricular fibrillation; nephritis, chronic	Much improved	24
2960	F	W	57	Dyspnea, edema	3–12	Not thickened	225–135	150–90	30	..	Alb. + Casts 0	Alb. 0 Casts 0	32	..	Auricular fibrillation; nephritis, chronic	Much improved	17
3016	F	W	63	Dyspnea, edema	2–9	Thickened	173–93	147–83	50	..	Alb. ++ Casts +	Alb. + Casts 0	27	..	Auricular fibrillation; nephritis, chronic	Much improved	11
4113	M	W	62	Dyspnea, edema	7–14	Thickened	210–130	160–95	45	48	Alb. ++ Casts ++	Alb. + Casts 0	..	..	Auricular fibrillation; nephritis, chronic	Much improved	60
4722	F	W	60	Dyspnea, edema	3–11	Thickened	260–115	180–100	22	33	Alb. + Casts +	Alb. 0 Casts 0	43	..	Myocarditis, chronic; diabetes	Much improved	35
3755	M	C	37	Dyspnea, edema	3–13	Thickened	162–83	133–75	33	57	Alb. + Casts +	Alb. + Casts 0	46	31	Mitral regurgitation; lues; nephritis, chronic	Much improved	40
3762	F	W	65	Dyspnea, edema	2–11	Thickened	200–116	150–86	40	..	Alb. + Casts +	Alb. 0 Casts 0	41	..	Myocarditis, chronic; nephritis, chronic	Much improved	14
2476	M	W	62	Dyspnea, edema	3–14	Not thickened	152–92	145–85	35	..	Alb. +++ Casts +++	Alb. + Casts 0	..	..	Diabetes; nephritis, chronic	Much improved	14
35746	F	W	49	Dyspnea, edema	2–10	Not thickened	200–85	148–70	30	..	Alb. + Casts +	Alb. 0 Casts 0	30	..	Myocarditis, chronic; nephritis, chronic	Much improved	15
35399	F	C	51	Dyspnea, edema	2–9	Thickened	230–150	185–115	34	..	Alb. ++ Casts ++	Alb. 0 Casts 0	51	38	Myocarditis, chronic; nephritis, chronic	Much improved	103

In the cases in this table with the vasomotor response also still retained as in Table I, but the cardiac and renal compensation both broken with the lowering, however, of the blood-pressure through vasodilatation, the strain on the struggling heart is greatly lessened, so that the fatigued muscles of the organ are given the opportunity of regaining their tone, with a resulting marked improvement in the cardiac decompensation and of the renal decompensation secondary to the weakened heart. Note the increase in the P. S. P. but the diminution in the N. P. N., as also in the amount of albumin and casts as denoted by the number of plus signs together with definite and in some cases marked improvement in the symptoms.

TABLE III.—VASOMOTOR RESPONSE REFRACTORY. BLOOD-PRESSURE IRREDUCIBLE. CARDIAC AND RENAL COMPENSATION MAINTAINED BY INTEGRITY OF CARDIAC MUSCLE.

Case No.	Sex.	Race.	Age.	Symptoms.	O.C.D.	Vessels.	Blood-pressure.		P.S.P.		Urine.		N.P.N.		Diagnosis.	Result.	Days observed.
							Entrance.	Discharge.	Ent.	Dis.	Entrance.	Discharge.	Ent.	Dis.			
2705	F	W	65	No decompensation	2–9	Thickened	193–103	223–93	53	48	Alb. 0 Casts 0	Alb. 0 Casts 0	33	..	Diabetes; nephritis, chronic	Compensation maintained	21
37320	M	C	46	No decompensation	2–9	Thickened	190–110	187–105	..	..	Alb. + Casts +	Alb. + Casts +	..	..	Nephritis, chronic	Compensation maintained	48
P	M	W	71	No decompensation	3–11	Thickened	176–120	213–113	..	..	Alb. + Casts +	Alb. + Casts +	..	..	Nephritis, chronic	Compensation maintained	8 yrs.
P	F	W	61	No decompensation	3–10	Thickened	175–80	180–105	..	..	Alb. 0 Casts 0	Alb. 0 Casts 0	..	..	Arteriosclerosis	Compensation maintained	1 yr.
P	M	W	65	No decompensation	3–11	Thickened	225–120	230–100	..	..	Alb. 0 Casts 0	Alb. 0 Casts 0	..	..	Arteriosclerosis	Compensation maintained	2 yrs.

In this group the hypertension is irreducible, but the heart is sufficiently strong to maintain the cardiac and renal compensation for a longer or shorter time at least, in spite of the increased strain thrown on it by the marked increase in blood-pressure, and just so long as the heart thus remains compensated do these cases continue symptomless.

TABLE IV.—VASOMOTOR RESPONSE REFRACTORY. BLOOD-PRESSURE RAISED THROUGH INCREASED TONE OF CARDIAC MUSCLE, WITH IMPROVEMENT IN CARDIAC AND RENAL DECOMPENSATION.

Case No.	Sex.	Race.	Age.	Symptoms.	O.C.D.	Vessels.	Blood-pressure.		P.S.P.		Urine.		N.P.N.		Diagnosis.	Result.	Days observed.
							Entrance.	Discharge.	Ent.	Dis.	Entrance.	Discharge.	Ent.	Dis.			
2589	M	W	57	Dyspnea, edema	8–19	Thickened; tortuous	145–85	183–100	15	49	Alb. ++ Casts ++	Alb. + Casts +	47	..	Auricular fibrillation; nephritis, chronic	Improved	30
2627	M	W	60	Dyspnea, edema	3–17	Thickened; tortuous	225–105	227–125	3	15	Alb. ++ Casts ++	Alb. + Casts +	63	58	Myocarditis, chronic; nephritis, chronic	Improved	30
2696	M	W	53	Dyspnea, edema	3–15	Thickened	205–148	213–123	19	29	Alb. ++ Casts ++	Alb. + Casts +	47	24	Myocarditis, chronic; nephritis, chronic	Improved	51
2945	F	W	40	Dyspnea, edema	4–15	Thickened; tortuous	168–130	188–138	18	37	Alb. ++ Casts ++	Alb. ++ Casts +	..	..	Myocarditis, chronic; nephritis, chronic	Improved	22
3808	M	W	55	Dyspnea, edema	3–10	Thickened; tortuous	160–120	190–100	35	..	Alb. + Casts +	Alb. 0 Casts 0	36	27	Myocarditis, chronic; nephritis, chronic	Improved	16

With the hypertension still irreducible a resulting break in cardiac and renal compensation had at last occurred, but the heart through rest or other treatment has so regained its tone as to raise the blood-pressure up again to the point necessary for compensation, with a consequent relief in the symptoms, more or less permanent. Note the increase in the P. S. P., the decrease in the albumin and casts. The hypertension, however, has not been conservative, but for a time destructive, and only necessary for compensation because of the loss of vasomotor response and compensation under such a strain cannot be for long maintained by the heart.

TABLE V.—VASOMOTOR RESPONSE REFRACTORY. BLOOD-PRESSURE LOWERED THROUGH IRREMEDIABLE CARDIAC DECOMPENSATION AND CONSEQUENT RENAL DECOMPENSATION.

Case No.	Sex.	Race.	Age.	Symptoms.	O.C.D.	Vessels.	Blood-pressure.		P.S.P.		Urine.		N.P.N.		Diagnosis.	Result.	Days observed.
							Entrance.	Discharge.	Ent.	Dis.	Entrance.	Discharge.	Ent.	Dis.			
2664	M	W	59	Dyspnea, edema	6-16	Thickened	232-112	185-140	12	2	Alb. +++ Casts ++	Alb. +++ Casts ++	63	100	Auricular fibrillation; nephritis, chronic	Death	18
2794	M	W	33	Dyspnea, vertigo	4-13	Thickened	212-140	160-97	9	0	Alb. ++ Casts ++	Alb. ++ Casts ++	97	200	Mitral insufficiency; nephritis, chronic	Death	60
2904	F	C	57	Dyspnea, edema	3-16	Thickened; tortuous	162-122	95-65	24	11	Alb. ++ Casts ++	Alb. ++ Casts ++	..	..	Myocarditis, chronic; nephritis, chronic	Death	55
2382	M	W	57	Dyspnea, edema	4-16	Thickened; tortuous	160-90	130-80	32	11	Alb. ++ Casts ++	Alb. ++ Casts ++	..	..	Myocarditis, chronic; nephritis, chronic	Not improved	85
2640	F	W	65	Dyspnea, palpitation	3-10	Thickened; calcareous	180-85	163-78	47	..	Alb. + Casts +	Alb. + Casts +	42	..	Myocarditis, chronic; nephritis, chronic	Not improved	15
2647	F	W	53	Dyspnea, edema	4-17	Thickened; calcareous	200-115	165-85	28	..	Alb. ++ Casts ++	Alb. ++ Casts ++	35	..	Auricular fibrillation; nephritis, chronic	Not improved	9
2748	M	W	54	Dyspnea, edema	4-15	Thickened	168-118	105-65	34	..	Alb. + Casts +	Alb. + Casts +	40	..	Mitral insufficiency; nephritis, chronic	Not improved	65
2957	F	W	64	No decompensation	3-15	Thickened	210-190	143-72	..	..	.....	.....	..	..	Diabetes	Not improved	28
2988	F	W	44	Dyspnea, edema	3-14	.....	222-118	205-130	46	..	Alb. ++ Casts ++	Alb. ++ Casts ++	19	..	Myocarditis, chronic; nephritis, chronic	Not improved	12
2997	M	W	62	Dyspnea, edema	2-13	Thickened; calcareous	153-100	140-90	16	..	Alb. ++ Casts ++	Alb. ++ Casts ++	44	..	Myocarditis, chronic; nephritis, chronic	Death	66
3822	M	W	54	Dyspnea, edema	4-16	Thickened; calcareous	170-75	143-60	Tr.	Tr.	Alb. ++ Casts ++	Alb. ++ Casts ++	29	46	Auricular fibrillation; nephritis, chronic	Death	15
3828	F	W	46	Dyspnea, edema	3-12	Thickened	260-162	212-143	47	40	Alb. ++ Casts ++	Alb. ++ Casts ++	47	45	Myocarditis, chronic; nephritis, chronic	Not improved	26
2589	M	W	57	Dyspnea, edema	7-19	Thickened	145-85	132-83	15	..	Alb. +++ Casts ++	Alb. +++ Casts ++	47	..	Auricular fibrillation; nephritis, chronic	Death	30
28137	M	W	54	Dyspnea, vertigo	4-17	Thickened	210-110	125-85	..	..	.....	.....	..	..	Myocarditis, chronic	Death	61

With the hypertension persistently irreducible this group of cases furnishes the sequel to the majority of those in Groups III and IV, for the pumping force of the heart becomes permanently crippled with a progressive increase of both cardiac and renal decompensation on to the fatal termination, since in this class of cases the reserve cardiac energy becomes exhausted when the organ is unable any longer to respond to remedial agencies. Note the definite lowering in blood-pressure due not to vasodilatation as in Tables I and II, but to cardiac failure, differing, however, from the drop in blood-pressure through vasodilatation as Table II in being permanent. Observe also the decrease in the P. S. P. with the increase in the P. N. P., as also in the albumin and casts. Also the failure of improvement in any of these cases, while at the same time the appearance of fatalities, for the first time in any of these groups, and which will exceed here 50 per cent. It is these final hopeless results of hypertension cases as embraced in this table which should so strongly plead for early control of high blood-pressure before the organic changes occur in bloodvessels, heart and kidneys that ultimately result in such disaster as depicted in this table.

CERTAIN CLINICAL ASPECTS OF PEPTIC ULCER

With Special Reference to Roentgen-ray Diagnosis as Observed in a Study of 743 Cases

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In a paper presented at the meeting of the Association of American Physicians in 1912, one of us presented a paper on a clinical study of 1000 cases of ulcer of the stomach and duodenum, and again in 1913 we presented our studies on the value of the *x*-ray in the diagnosis of this affection. Since then a further series of 743 cases has been studied by us; not only have these cases been followed clinically, but a careful *x*-ray study was made in every instance. The method followed was identical with that published in our former paper.

TABLE I.—ILLUSTRATING THE INCIDENCE OF IMPORTANT SIGNS AND SYMPTOMS IN 743 CASES OF PEPTIC ULCER.

	Cases proved by operation.	Undoubted cases of ulcer not confirmed by operation.	Somewhat doubtful cases.	Total.
	185	323	235	743
Definite history of ulceration	163	301	158	622
Pain	169	297	221	681
Tenderness	160	293	188	641
Vomiting	116	208	166	480
Hematemesis	32	67	89	188
Melena	89	155	101	345
Occult blood	103	205	108	421
Normal acidity	54	120	41	215
Hyperchlorhydria	68	95	77	240
Hypochlorhydria	42	62	31	135
Positive *x*-ray findings	147	272	210	629

The cases were first gone into clinically, and then without any note being given as to the nature of the disorder were sent for *x*-ray examination. The two reports were then placed side by side in order to determine how closely the clinical and *x*-ray diagnoses corresponded.

The 743 cases may be divided into three groups:

Group I. Cases in which there was an operation, and in which the diagnosis was definitely proved. There were 185 of these cases.

Group II. Cases which presented such typical clinical symptoms as well as positive *x*-ray signs of peptic ulcer that the correctness of the diagnosis was positive. These cases numbered 323.

Group III. Somewhat doubtful cases which presented many of the signs and symptoms of ulcer, but lacked some important signs. In the larger number of these cases the *x*-ray findings were quite definite. There were 235 of these cases.

Group I. This group represents the most important in this series of ulcer cases, inasmuch as the diagnosis was definitely confirmed in all instances by operation. It is of interest to note the incidence of the clinical signs in these cases.

Of the 185 patients, 132 were males and 53 females. Table II shows the number of cases observed in males and in females according to age.

TABLE II

Years.	Males.	Females.	Total.
10 to 20	26	4	30
20 to 30	44	11	55
30 to 40	36	32	68
40 to 50	21	3	24
50 to 60	5	3	8

Of the 185 cases, a direct history of ulcer was present in 163 (88 per cent.); pain in 169 (90 per cent.); a tender epigastric area in 160 (86 per cent.); vomiting in 116 (63 per cent.); hematemesis in 32 (17 per cent.); melena in 89 (48 per cent.). The stools were examined for occult blood in 128 instances, the findings being positive in 108 (84 per cent.).

Of the 185 cases, the gastric secretion was examined in 164.

Normal acidity was observed in . . . . . 54 cases or 32 per cent.
Hyperchlorhydria was observed in . . . . 68 cases or 41 per cent.
Hypochlorhydria and anacidity in . . . . 42 cases or 26 per cent.

The percentage of cases of hyperchlorhydria in the series greatly exceeds that in our former series, which is due to the fact that many of these cases were examined by means of the Rehfuss fractional method and thus in many which apparently had presented a normal acidity or subacidity there was in fact hyperacidity.

The *x*-ray findings in this series of cases are very interesting, inasmuch as the results were definitely checked up by operation.

In the 185 cases of ulcer the diagnosis as made by the *x*-rays was verified in 147 (79.4 per cent.). Of these 147 cases, in 68 the ulcers were duodenal (46.2 per cent.), in 53 gastric (36 per cent.), in 17 pyloroduodenal (11.5 per cent.); in the remaining 8 (5.2 per cent.) the location of the ulcer was undetermined. In these 8 cases no constant filling defect was obtained, but the functional activity of the stomach was so characteristic that there was no doubt as to the nature of the lesion. Attention will later on be drawn to the importance of this finding, even when no persistent filling defect is revealed.

There remain 38 cases (20 per cent.) in this series in which the *x*-ray findings were either not characteristic or pointed to other conditions.

Of these there was nothing abnormal revealed in 7 instances; in 21 the diagnosis of gall-bladder adhesions was made; in 5, of chronic appendicitis and adhesions in the cecal region, and in 5 the whole picture suggested an enteroptosis. In the 21 cases suggesting gall-bladder adhesions there were filling defects in 8, but these gave the impression of being produced by adhesions and not by ulcer; in 5 instances the diagnosis seemed uncertain, but evidences pointed rather to the gall-bladder, and in the remaining 8 instances the findings were definitely those of a gall-bladder affection.

Group II. In this group are included those cases which presented such typical clinical signs as well as positive *x*-ray findings of ulcer that the diagnosis could hardly be questioned. There were 323 cases in this group. Table III shows the number of these cases observed in males and in females according to age.

In this group of 323 cases there were 301 presenting definite ulcer histories (93 per cent.); pain was present in 297 cases (91 per cent.); a tender epigastric area in 293 (90 per cent.); vomiting in

208 (61 per cent.); hematemesis in 67 (20 per cent.); melena in 155 (48 per cent.). The stools were examined in 255 instances for occult blood, which was found present in 205 (81 per cent.).

TABLE III

Years.	Males.	Females.	Total.
10 to 20	14	22	36
20 to 30	21	57	78
30 to 40	28	79	107
40 to 50	39	10	49
50 to 60	32	8	40
60 to 70	13	0	13
	147	176	323

Of the 323 cases, the gastric secretion was examined in 277 instances.

Normal acidity was observed in	120 cases or 43 per cent.
Hyperchlorhydria was observed in	95 cases or 33 per cent.
Hypochlorhydria and anacidity in	62 cases or 24 per cent.

X-ray findings in this group were even more definite than in Group I. Of the 323 cases, positive *x*-ray findings were obtained in 272 (84 per cent.).

Of these 272 cases, 117 were duodenal ulcers (43 per cent.); 109 gastric ulcers (40 per cent.); 38 pyloroduodenal ulcers (14 per cent.) and in 8 (3 per cent.) the location remained undetermined. A filling defect was absent in the 8 undetermined cases; but here too the functional activity of the stomach was so definite that a positive diagnosis of ulcer was made with almost absolute certainty.

There were 51 cases (15.6 per cent.) in this group in which the *x*-ray findings were either uncertain or pointed to some other pathological conditions.

Of these cases no abnormality was discovered in 12 instances; in 29 the diagnosis of gall-bladder adhesions or of a chronic appendicitis was made. In the 29 cases a filling defect was observed in 11, which was regarded as due to adhesions and not to ulceration; notwithstanding these *x*-ray findings the clinical signs were so definite that the diagnosis of ulcer appeared justifiable.

Group III. We have put in this group those cases that presented many of the manifestations of ulceration, but in which there

still appeared some element of doubt as to diagnosis. In some of these cases there were few clinical signs except hemorrhage, while the *x*-rays pointed to ulcer; in other cases the clinical signs indicated ulceration, while the *x*-rays either revealed no lesion in the stomach whatever or else pointed to some affection in a more distant portion of the abdominal cavity. In no inconsiderable number of cases the history of ulceration was so definite that the diagnosis appeared unmistakable; yet the gastric secretion presented an absence of free hydrochloric acid, there was no history of hemorrhage, nor was occult blood found in the stools at repeated examinations.

The diagnosis was definitely cleared up in many of these instances by positive *x*-ray findings.

Table IV presents the cases of ulceration observed in this group, in males and in females, arranged according to age. Of the 235 patients 121 were males and 114 females.

TABLE IV

Years.	Males.	Females.	Total.
10 to 20	4	6	10
20 to 30	15	8	23
30 to 40	29	49	78
40 to 50	37	28	65
50 to 60	32	15	47
60 to 70	4	8	12

In this group of 235 cases there were 158 presenting a definite ulcer history (67 per cent.); pain was present in 221 cases (94 per cent.); a tender epigastric area in 188 (80 per cent.); vomiting in 156 cases (66 per cent.); hematemesis in 89 (37 per cent.); melena in 96 (40 per cent.). The stools were examined in 133 instances for occult blood, which was found present in 108 (81 per cent.).

Of the 235 cases, the gastric secretion was examined in 149.

Normal acidity was observed in	41 cases or 27 per cent.
Hyperchlorhydria was observed in	77 cases or 51 per cent.
Hypochlorhydria or anacidity in	31 cases or 22 per cent.

In this group of 235 cases the *x*-ray findings were so outspoken in 210 instances (89.7 per cent.) that, notwithstanding the absence of certain of the clinical signs, the diagnosis of ulcer seemed justified. Of the 210 cases in 80 (38 per cent.) there were duodenal ulcers;

in 88 (42 per cent.) gastric ulcers; in 25 (11 per cent.) pyloroduodenal ulcers, and in 17 (8 per cent.) the location of the lesion remained undetermined. In these 17 cases a filling defect was not observed, yet here too the functional activity of the stomach was so characteristic that there remained but little doubt as to the diagnosis. There remain 25 cases in this series (12 per cent.) in which the *x*-ray findings were not characteristic of ulcer or else pointed to other conditions. Of these nothing abnormal was observed in 8 instances in the plates; in 9 gall-bladder adhesions were shown, and in 8 chronic inflammatory changes in the right lower quadrant indicating the presence of a chronic appendicitis.

The *x*-ray findings in uncomplicated cases of gastric and duodenal ulcer are, as a rule, very definite as well as constant. The signs ordinarily observed are not unlike those described by us in a former communication.

It is only within the last years that we are beginning to observe results upon which reliance may be placed. The old theory that it was possible to diagnose ulcer from the adherence of bismuth to the raw surfaces has now been practically abandoned, inasmuch as experience has taught us that this rarely happens because the irritability of the raw surface produces hypermotility with violent contractions, which render it almost impossible for the bismuth to adhere to the raw surfaces. At present we lay stress on the way the stomach and intestines function as well as upon the actual demonstration of the ulcer. Curiously enough, the diagnosis of duodenal ulcer is much simpler than that of gastric ulcer.

We can practically always rule out the presence of a simple duodenal ulcer, but we cannot always rule out gastric ulcer. The main distinction lies in the fact that in an irritating lesion of the stomach, such as ulcer, the consequent hypermotility causes a tonic contraction of the pylorus with retention of the gastric contents over a shorter or longer period, as well as a deformity, according to the situation of the ulcer. On the other hand, in lesions of the duodenum we have indeed a hypermotility not only of the duodenum, but of the stomach itself; but in this case we do not have the spastic condition of the pylorus, consequently the hypermotility produces a rapid emptying of the stomach contents. For example, in our experience,

in simple ulcer of the duodenum not complicated by adhesions, we find that the stomach will invariably extrude the greater part of its contents in from fifteen or twenty minutes to an hour. There are in addition certain characteristic features connected with this lesion; we have a decided hypermotility, but the contractions are quite uniform, and there is no tendency toward hour-glass formation of the stomach. The pylorus is patulous and the bismuth flows quite freely into the duodenum. The duodenum is in very active contraction, and in many cases we find that there is a deformity in some portion of it, and this defect persists throughout the period of the examination. At times we may observe bismuth along either side with the defect between the two bismuth currents.

In gastric ulcer we have just the reverse. There will be primary quick expulsion of contents and then the spastic condition of the pylorus appears with hour-glass formation, and we have a retention, lasting anywhere from four to six hours, according as the lesion is simple or is complicated by adhesions. In addition, a filling defect is usually observed which remains constant in all examinations.

The differentiation between gastric and duodenal ulcer from clinical signs alone is often very difficult, and not a few clinicians hold that in many instances it is impossible. The *x*-ray findings in the two conditions, however, differ so markedly that in them we possess an almost positive means of differentiation.

In our combined series of cases positive *x*-ray findings were noted in 84.4 per cent. of all cases examined. Of these, 42 per cent. represented duodenal ulcers; 39 per cent. gastric ulcers; 12 per cent. pyloroduodenal ulcers; in 8 per cent. the location of the lesion was undetermined.

While the functional activity of the stomach from a roentgenological point of view may indicate the presence of an ulcer, the filling defect or deformity may be absent and may not be revealed in the plates, owing to the fact that only when the lesion is situated on the anterior surface of the stomach and along the anterior surface of the lesser and greater curvatures can this condition be observed. According to our observations the functional signs are often as important as the presence of the defect in arriving at defi-

nite conclusions. This condition is especially well illustrated in the healing of ulcers (attention to which will be called later on), in which, although the defect may still remain in the form of a cicatrix, the functional activity of the stomach may have become entirely normal.

In 8 per cent. of our cases there were no defects observed, yet the functional activity of the stomach pointed definitely to ulcer.

The greatest difficulties arise in the diagnosis of complicated cases; that is, when adhesions are present, due either to the healing of the ulcer or to inflammations connected with one or other of the organs in the abdominal cavity. These adhesions so frequently mask the usual findings that it is often impossible to determine whether we are really dealing with an ulcer or whether a lesion of some other organ is causing the symptoms. Such adhesions may arise from the ulcer itself, from the gall-bladder or appendix, or there may be no adhesions at all in the region of the stomach, and the gastric findings may be due to a purely reflex condition or to spasm.

It is necessary at times, in a certain proportion of cases in which adhesions of the stomach are present, to lay special stress upon the clinical history of the case before a final decision can be made. If the clinical signs coincide with a definite history of ulcer, we must conclude that the adhesions have taken their origin from the ulcer; if of cholelithiasis, from the gall-bladder; and so on, inasmuch as from a roentgenological point of view the appearances are frequently identical.

In 9 per cent. of the cases in our series the diagnosis was rendered doubtful by the presence of adhesions.

As has been pointed out, unless due care be exercised, one may easily be misled by certain reflex or spastic conditions of the stomach. It is not uncommon to observe a stomach presenting a persistent filling defect in a definite area and continuing over a period of an hour or two—in a single instance under our observation it persisted for forty-eight hours. In doubtful cases, spasm of the stomach can easily be eliminated by the administration of full doses of atropin for one or two days, until the patient is well under its influence. A second examination, made under these conditions, will immediately

show that the suspicious area has completely vanished, and that the condition previously observed was due to spasm.

Additional evidence of the presence of an ulcer when situated at or near the pylorus is the presence of obstructive signs produced by the cicatrix while the ulcer is healing.

Clinically, the diagnosis of *gastrectasia due to stenosis of the pylorus* is usually not difficult, especially when the cardinal symptoms of this disease are present. The vomiting of the collective type, together with peristaltic or antiperistaltic waves, suggests the diagnosis; and this becomes even more certain when remnants of food are obtained from the fasting stomach in the morning, and especially when the gastric contents are of the three-layered variety, and contain numerous sarcinæ; or when the rice test of Hausemann or the chlorophyl test of Boas is positive. But we all know that these findings are present only when the obstruction is marked or nearly complete, and that there are a large number of cases in which obstruction is suspected, and yet many weeks often elapse before the stenosis becomes sufficiently marked to warrant a positive diagnosis, for the symptoms already noted occur only as late manifestations of the disease, and are not present or are observed only occasionally as early signs. At times spastic contractions of the pylorus due to former ulcers or the irritation exerted by the gastric contents upon erosions and fissures in this region afford similar signs.

In this condition, when the *x*-ray examination is made, a typical sac-like formation is observed, and all the bismuth rests at the bottom of the fundus. Under such conditions the examination will show a retention of contents for from ten to twenty hours.

In the early stages of gastrectasia, that is, when the obstruction is still incomplete, the diagnosis is often very difficult. The condition is due to a partial stenosis of the pylorus, and inasmuch as the symptoms produced by it are quite vague, the condition is often overlooked or an incorrect diagnosis is made.

The physical signs of the disease are not marked, peristalsis being usually absent and vomiting occurring irregularly, the vomitus being devoid of the usual features occurring in gastric stasis. A symptom very frequently present is pain, appearing some time after

meals and becoming most intense two or three hours after the ingestion of food.

This plan is due to the pyloric spasm produced by the incomplete obstruction, and is temporarily relieved by the ingestion of food or of alkalies. As is well known, this symptom is characteristic of ulcerative lesions in the pyloric or juxtapyloric region, but since in many instances partial obstructions have their origin in pyloric and juxtapyloric ulcerations, this symptom is valuable as an early sign of the disease. As additional evidence of the presence of partial stenosis is the existence of gastric secretion in the fasting stomach, especially if it is observed in frequent examinations. If the fasting stomach is constantly empty of gastric secretion, partial stenosis may usually be excluded. The diagnosis may be based, therefore, on the presence of secretion in the fasting stomach, occurring continuously or intermittently, together with stasis, even of a small amount, appearing at more or less frequent intervals.

These signs appear, however, so intermittently that they are often overlooked, especially when overshadowed by the usual symptoms of dyspepsia occurring in this affection. The *x*-ray has given us a means of more thoroughly solving this difficult problem.

In the early stages of this condition we have active contractions with the slow extrusion of the stomach contents. Now a normal stomach extrusion gets rid of its bismuth meal in from three to six hours. Generally, we observe that the high stomach occupying the horizontal position empties itself much more quickly than the fish-hook variety, so that it might be stated that three or four hours is the normal rate of emptying for the horizontal stomach, and from five or six hours for the prolapsed fish-hook variety. When in these various types we note that while the contractions are good, but the expulsion of contents is slower than under normal conditions, we must consider the possibility of some beginning obstruction.

A second very significant sign is the fact that in the study of the plates we frequently observe that a portion of the stomach just within the pylorus on the greater curvature in the prepyloric region shows a tendency to bulge. This condition is produced by the active contraction of the stomach, forcing all the food toward the pyloric region. The pylorus not being patent, the prepyloric portion of the

stomach becomes dilated under this constant pressure, so that the plate presents the pylorus not at the end of the stomach, as it were, but with the prepyloric region extending further to the right than the pylorus, the pylorus resting on the top of the stomach and pointing to the splenic region. The prepyloric bulging is dependent largely upon the duration of the affection. In early cases it is very slight, but as the condition advances the prepyloric bulging may reach the size of a hen's egg. If the condition persists, dilatation begins to take place, and after a time practically the entire fundus yields, so that a typical sac-like formation is produced, and all the bismuth rests at the bottom of the fundus.

In 20 per cent. of our cases there were evidences of obstruction with dilatation of the stomach; in 12 per cent. of these partial obstruction was observed.

In a certain number of cases there are definite clinical evidences of ulceration, and yet the *x*-ray presents no indication whatsoever of this condition. This may be due, as we have already pointed out, in some instances, to adhesions masking the true condition, but the absence of definite *x*-ray signs cannot always be traced to this factor. It happens at times that a complicating chronic appendicitis or cholecystitis may be so marked as to mask any findings in the stomach itself, and the significance of a small filling defect might easily be overlooked.

In one of our cases (Dr. B.), a man of sixty-four years of age, who had presented definite clinical signs of duodenal ulceration for years, and in whom the *x*-ray findings had been positive four years previously, our examination gave evidence of gall-bladder adhesions and no signs of ulceration. At operation a large duodenal ulcer with adhesions was found. In another instance (Mrs. B.) the *x*-ray findings pointed to a chronic appendicitis, whereas the clinical evidences were definitely in favor of ulcer. At operation a definite indurated duodenal ulcer was found.

In our entire series there were 3 per cent. of cases of ulceration in which the *x*-ray signs gave no evidences of the actual condition, and in 15 per cent. they were indefinite.

Although ulcerations are not always revealed by *x*-ray examinations, there are many cases of ulcer doubtful from a clinical stand-

point in which the ray will clear up the diagnosis. In 2 of our cases the clinical signs were indefinite, but suggested an appendicitis; the *x*-ray was definite as to ulcer in both instances. Appendectomy was performed, and only temporary relief was afforded; there was subsequent gastric hemorrhage and finally operation revealed an ulcer in each instance. Another patient (Mr. McE.), a man aged sixty-six years, gave a history of very indefinite gastro-intestinal symptoms. The *x*-ray revealed ulceration; a sudden large gastric hemorrhage showed the correctness of this finding. The *x*-ray is, therefore, of the greatest help in pointing to the current diagnosis in doubtful cases. In 1 per cent. of such indefinite cases in our entire series the *x*-ray cleared up the diagnosis.

There are cases, however, in our experience in which the diagnosis of either chronic appendicitis or cholelithiasis is made not only from a clinical, but also from a roentgenological standpoint, but which at operation present no evidence of such conditions, ulceration of the stomach or duodenum being found, although the *x*-ray plates have shown no evidences pointing to either affection. Finally, there still remains another group of cases in which the ulcerations are of the so-called mucous type. These are easily demonstrated by means of the *x*-ray, but are rarely observed at operation unless the stomach itself be incised. It frequently happens that such cases come to operation, and yet no abnormality is observed at the exploration. This is due to the fact that while both mucous and penetrating ulcers are alike easily discernible by means of the *x*-ray, we have as yet no means of distinguishing between such conditions, except in those instances in which large indurated or perforating ulcers are present.

In the *x*-ray study of *gastric ulcer* the differential diagnosis between this condition and *gastric carcinoma* is often very difficult. It is still a much-debated question whether carcinoma of the stomach has its origin primarily as such, or is the result of a transition from an ulcer. If the latter view be correct, one can readily understand the difficulty in determining when the benign condition enters the stage of transition into malignancy. The situation of both ulcer and carcinoma is very frequently the same, although we observe ulcer more frequently than carcinoma on the lesser curvature.

In the differential diagnosis between the two conditions the points to be taken into consideration are as follows:

1. *Peristalsis.* In ulcer there is always hypermotility with a spasm of the pylorus and more or less retention of contents. In carcinoma, unless there is obstruction, there is always hypermotility with rapid evacuation of contents.

2. *Position.* Ulcer is generally observed on the lesser curvature near the pylorus, although it may occur on the greater curvature and is frequently found in the duodenum. Carcinoma may occur in any part of the stomach. The invasive lesions are more frequently seen on the lesser curvature near the pylorus and less frequently on the greater curvature. The massive growths are more generally seen on the greater curvature.

Filling Defect. In ulcer the filling defect is much smaller and is not apt to have the immediate peristaltic waves interfered with, although, if the inflammatory area be large, there may be a dead area surrounding the filling defect. In carcinoma the filling defect is generally surrounded by an invasive area, which, although not appearing on the plate, interferes with motility, producing an apparently large dead area. In ulcer of the pylorus there is a filling defect, but it does not generally assume a crater-like appearance. Carcinoma of the pylorus in the earliest stage is generally annular and produces a crater-like appearance.

When any of these conditions passes on to the obstructive stage, the change that is caused by the dilatation may mask the signs associated with the filling defect.

In our experience, in the very early stages of gastric cancer, it is frequently impossible to determine whether we are dealing with a malignant or a simple ulceration. Our main aim, however, is to decide whether the lesion at hand is really an ulcer or not. Inasmuch as indurated gastric ulcers have at times a tendency to become malignant and produce roentgenograms similar to those which are cancerous, they must be included in the same class. The exact diagnosis must be cleared up by further investigation into the clinical history and by the examination.

But even under these conditions there are many cases in which the diagnosis may still remain in doubt until operation, and, in some,

microscopic examination of the specimen after removal may be necessary in order to establish the true nature of the disease.

In our series there were 1.1 per cent. of cases in which the ulcer was mistaken for carcinoma; in a larger percentage, however, carcinoma was mistaken for ulcer.

Now that we have taken up the positive phase of the diagnosis of ulcer, it is wise to draw some conclusions as to the *negative findings*. In the first place, we believe that we can rule out positively the presence of a duodenal ulcer. If we observe that the stomach contents are not expelled promptly, and that the greater portion remains after the lapse of an hour, we can maintain confidently that the trouble is not in the duodenum. Even in the old chronic ulcer, with adhesions, the motility is so marked that it cannot be overlooked. The negative diagnosis of gastric ulcer is also of importance. However, so many complicating phases are present in these cases that the retention of bismuth in the stomach does not appear to have quite the same significance as the hypermotility in duodenal ulcer. The absence of a filling defect in the stomach or of a deformity of the duodenal cap is a significant sign pointing against ulcer.

As has been shown, in gastric ulcer, we have a spastic retention. In simple atony and in prolapse we may have retention, and yet the spastic character of the retention is not present, nor is there any tendency toward the formation of an hour-glass stomach.

The absence of any of the positive signs of ulcer by means of the *x*-ray examination has been of the greatest help to us in excluding the presence of ulcer. This method has been especially helpful in the diagnosis of atypical conditions and affords us the most positive method of excluding ulcer.

There have been 698 cases in which we have been able to exclude the presence of ulcer by this method of examination.

Another very important point which our *x*-ray studies have brought out in connection with ulcer is that the degree of healing can be determined by this method. We were among the first to call attention to the fact, and other clinicians have since corroborated this finding. In ulcer, when the patient is given a rest-cure treatment, all symptoms gradually disappear and the patient becomes, comparatively speaking, well. This usually takes place in from four

to five weeks. At the end of this time, however, if a second bismuth examination is made, we often find the same characteristic signs as in the first ulcer, though the patient shows no symptoms whatever.

In a series of ulcer cases, that have been examined in from three to four weeks after an absence of symptoms, we have frequently found but little change in the defect or motility of the stomach.

When these patients are given the ordinary diet these symptoms may recur in a short time. If treatment is continued, however, our experience has demonstrated that, as the ulcer continues to heal, the motility of the stomach returns to a more normal condition, and by making repeated *x*-ray observations over a long period of time we can observe when the ulcer has healed.

There can be no question that this is one of the most important findings of this work, inasmuch as, until this method was employed, there was absolutely no means of determining whether an ulcer had healed or not. Our only means of determining this question has been a return of symptoms when the patient was placed upon an ordinary diet, and this simply meant a relapse for the patient. By means of the *x*-ray examination made from time to time we are enabled to determine the progress of healing. This method has been utilized to great advantage by us in 321 of our cases (43 per cent.).

There is another fact of great importance connected with the healing of ulcers brought out by this method of examination. We observed that not infrequently, after an ulcer has completely healed, another ulcer may take its origin, sooner or later, either at the same location or at another, either in the stomach or duodenum. This finding was demonstrated by us in 64 instances (8 per cent.). In the largest number of these cases there can be but little question that the ulcer must have been caused by some focal infection for, curiously, in some instances after the removal of the infection there was no further recurrence.

Finally, important evidence is further obtained by means of the *x*-ray as to the extent of the ulcer and degree of induration, as well as the degree of obstruction, and thus we are guided in determining in a measure whether surgical interference should or should not be undertaken. Of the 185 of our cases which were operated on, the

x-ray demonstrated the necessity of the operation in 147 cases (79.4 per cent.).

Conclusions. From our studies on the many cases of peptic ulcer in which *x*-ray examinations were made, we believe that we are justified in drawing the following conclusions:

1. The *x*-ray offers most valuable assistance to the diagnosis of peptic ulcer, and although this method is not yet sufficiently well developed to be relied upon alone without entering into the clinical aspects of the disease, it is of the greatest diagnostic help in obscure cases.

Positive *x*-ray findings are noted in about 84 per cent. of cases of peptic ulcers and in 79 per cent. of cases operated upon.

2. In duodenal ulcer there is excessive hypermotility of the stomach with rapid evacuation of the contents, so that the greater portion is extruded within the first half hour; there is hypermotility of the duodenum with formation, usually, of a deformity which remains fixed in all the examinations.

3. The diagnosis of gastric ulcer is dependent upon two conditions, namely, the functioning of the stomach and the finding of the filling defect. It is only when the filling defect is situated along the anterior surface of the stomach and along the anterior surface of the lesser and greater curvatures that it can be demonstrated. On the other hand, it matters not what the situation of the ulcer is, the functions of the stomach are materially affected. We have in this condition an excessive irritation from the ulcer, with consequent retention and a spastic condition of the pylorus, so that for the time being there is practically no expulsion of bismuth. It is only when the spasticity relaxes that a portion of the bismuth is expelled. In gastric ulcer, wherever its situation, we can always look for a certain amount of retention of contents. There is always a more or less marked hour-glass formation. According to our observations the functional signs are often as important as the presence of the filling defect in arriving at definite conclusions, inasmuch as in 8 per cent. of our cases, although there were no defects found, the functional changes pointed definitely to ulcer.

4. The greatest difficulties arise in the diagnosis of complicated cases; that is, when adhesions are present. These so frequently

mask the usual findings that it is often impossible to determine whether there is really an ulcer of the stomach at hand or a lesion of some other organ. When the ulcer is situated at or near the pylorus, signs of partial obstruction frequently aid in establishing the diagnosis.

5. The *x*-ray affords an almost absolute means of differentiating between gastric and duodenal ulcer.

6. By means of the *x*-ray examination we can generally rule out the presence of ulcer.

7. We can approximately determine the degree of healing as well as the recurrence of an ulcer which cannot be as certainly determined in any other way.

8. One can obtain sufficient evidence as to the extent and induration of the ulcer and degree of obstruction to guide us, in a measure, as to the necessity of surgical intervention.

THE PATHOGENESIS OF INFANTILE SCURVY

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For some years we have been studying various aspects of the symptomatology and dietetics of infantile scurvy. In a recent paper[1] it was shown that pasteurized milk brings about this disorder in some cases unless an antiscorbutic food is included in the dietary. The type of scurvy induced under these conditions, as noted elsewhere, is not the text-book variety of this disease, but what has been termed latent or subacute scurvy, characterized by anemia and pallor, failure to gain in weight, rapidity of pulse and respiration, tenderness of the bones, and by a sharp recession of all these signs and symptoms when orange juice or other antiscorbutic foodstuff is given. In asserting that scurvy is brought about by pasteurized milk it should be emphasized that this is not synonymous with saying that this disorder is caused by heating the milk to the temperature of pasteurization. It is for this reason that we have, in this connection, referred to pasteurized milk rather than to pasteurization, as the former term includes not only the heating process, but the handling, subsequent cooling, aging and other factors.[2]

Some have questioned whether pasteurized milk is really involved in the production of scurvy. The fact, however, that when one gives a group of infants this food for a period of about six months, instances of scurvy occur, and that a cure is brought about when raw milk is substituted, taken in conjunction with the fact that if we feed the same number of infants on raw milk, cases of scurvy will not develop —these results seem sufficient to warrant the deduction that pasteurized milk is a causative factor. The experience in Berlin, noted by Neumann[3] and others, is most illuminating and convincing in

this connection. In 1901 a large dairy in that city established a pasteurizing plant in which all milk was raised to a temperature of about 60° C. After an interval of some months infantile scurvy was reported from various sources throughout the city. Neumann[3] writes about the situation as follows: "Whereas Heubner, Cassel and myself had seen only 32 cases of scurvy from 1896 to 1900, the number of cases suddenly rose from the year 1901, so that the same observers—not to mention a great many others—treated 83 cases in 1901 and 1902." An investigation was made as to the cause, and the pasteurization was discontinued. The result was that the number of cases decreased just as suddenly as they had increased. It should be added that the milk was also brought to the boiling-point in the home, as is the custom throughout Germany.

For two years the milk which we used at the infant asylum was pasteurized commercially at 165° F. for thirty minutes; for two subsequent years the dealers raised it to a temperature of only 145° F. for thirty minutes. According to our experience, milk heated to the higher degree of temperature induces scurvy more readily than that which is brought to only 145°, judging by the results of the four-year period. During the past year we have bought raw certified milk, the best milk which is sold in the city, and pasteurized it in the institution at 145° for thirty minutes. Various formulas were prepared with this milk, so that should any disorder develop we might be in a position to analyze the trouble and correct the dietary defect. Among six infants given milk which was pasteurized and prepared for feeding on the morning it was received, none developed scurvy. One infant in our institution who had been receiving commercially pasteurized milk for many months and who showed symptoms of subacute scurvy improved on this home pasteurized milk. It may be said, therefore, that this milk manifested almost no tendency to produce scurvy. How, then, did it differ from the commercially pasteurized milk which we had previously been buying? It differed mainly, so far as we can judge, in the interval which elapsed between the heating process and the consumption of the milk. In New York City the major portion of the bottled milk is Grade B, most of which is pasteurized after it reaches the city, soon after midnight; fully two-thirds of this

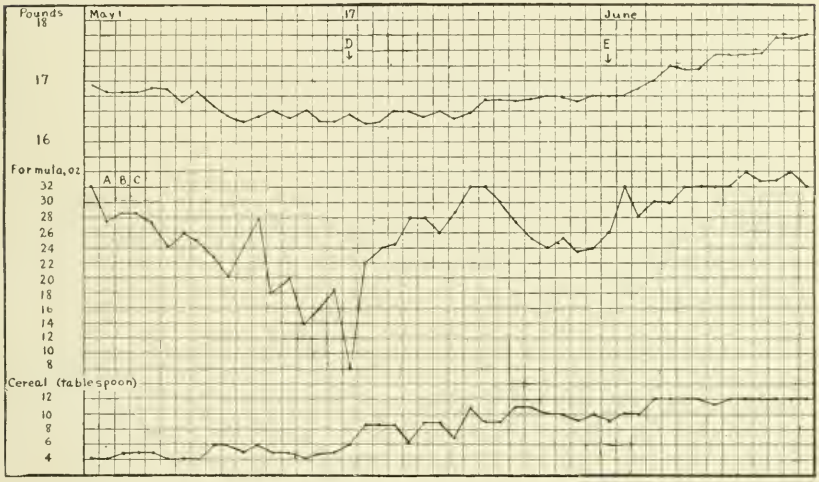
milk is delivered to the consumer the same morning on which it is pasteurized; however, part of it is held over and delivered twenty-four hours later. The better milk, Grade A, is largely pasteurized in the country, so that an interval of twenty-four hours elapses between the heating and the delivery.[4] In order to reproduce these conditions, we held over some of the pasteurized milk for twenty-four hours on ice, so that it corresponded more closely to Grade A milk. Of eight infants who received formulas made with this type of milk (Pasteurized II), two showed scorbutic signs which promptly yielded to orange juice. In one of them the onset seemed to have been precipitated by an intercurrent infection of "grippe." Although these results point to the influence of the freshness or staleness of pasteurized milk, they likewise indicate that aging must be considered only a mild scorbutic agent. This deduction is forced on us by the mild nature of the scorbutic process, by the paucity of cases developing, and by the further observation that among eight other infants who were given the milk which had been kept on the ice for forty-eight hours following pasteurization (Pasteurized III), only two evinced symptoms of subacute scurvy. That aging affects raw milk similarly was shown by the fact that one baby developed latent scurvy among a group of four who were receiving Raw III milk, that is, certified milk which was kept for forty-eight hours on the ice before preparing the formula. This infant developed an eczematous skin condition, to which we have drawn attention before, and which we have frequently noted in association with scurvy. When orange juice was given the skin lesions disappeared, the general condition improved, and there was a marked gain in weight.

That the degree of heat to which the milk is subjected is not an all-important factor in rendering the dietary unsuitable was clearly shown in the cases of some infants that received milk which had been boiled for a period of five minutes. After an interval of five months one well-nourished infant, aged eleven months, and weighing $18\frac{1}{2}$ pounds, showed pallor, some periosteal tenderness, slight peridental hemorrhage and a rapid pulse. These symptoms were alleviated by a substitution of raw milk. It is furthermore evident from the reports of others that boiled milk cannot be an important etiological

factor in bringing about a scorbutic condition. When we consider the thousands of infants that receive milk of this kind and thrive, and that a moderate number must be deprived of orange juice or other antiscorbutic food, we must realize that boiled milk can lead to scurvy only in a mild degree. Statistics such as those of Variot,[5] who has distributed in his out-patient department during a period of twelve years 400,000 quarts of sterilized milk (heated in the half liter bottles and hermetically sealed at the farm) without observing a case of scurvy, must be accorded weight in this connection. It is to be noted, however, that Variot remarks that these infants frequently develop anemia unless additional diet is given, so that it must be considered open to question whether careful and repeated examinations (such as can be carried out only at home or in an institution) might not have uncovered some of the minor manifestations of scurvy. Of course, unless it is certain that these infants were receiving only sterilized milk, and absolutely no other food, for a period of at least six months, they cannot be considered as affording a test of the question.

Four infants were given the milk for forty-eight hours after it had been boiled, and in one instance inconclusive signs of scurvy developed. That aging, however, may also play a role in relation to the use of sterilized milk is well illustrated by some cases in the literature where babies developed scurvy on sterilized milk which had been sent to the country, and where they recovered on receiving the same milk freshly sterilized. In some of these instances the milk was some weeks old. There is a point, one which is lost sight of, which should be emphasized in connection with a discussion of the role of heated milk in the causation of scurvy. It is taken for granted that if pasteurization will induce scurvy, heating the milk to a still higher degree will certainly lead to this more surely and constantly. This deduction is by no means warranted. Indeed, from personal experience, it would seem that *milk which has been boiled is less apt to induce scurvy than milk which has been pasteurized*, heated to 165° or a lower temperature. This was well illustrated by putting four infants, who were receiving freshly pasteurized milk, on "evaporated milk," so-called because in the course of heating for five to six hours it had been reduced to one-quarter its volume. It thus

resembled in many respects the evaporated milk to be bought in the market. In preparing the formulas for these infants due cognizance was taken of the concentration of fat, sugar and proteins of the milk. This food was well taken by the babies, and after a period of five months none manifested signs of scurvy.



Joseph G., aged nine months. Chart showing stationary weight in spite of marked variation of fluid intake (due to oliguria followed by diuresis). *A* = Schloss milk; *B* = cod-liver oil; *C* = egg yolk; *D* = 1 ounce of orange juice; *E* = potato (orange juice stopped).

As it has been claimed that scurvy is an acidosis, brought about by a long-continued diet of high acidity, the reaction of the various diets was recorded. This is given in Table I. It will be seen that pasteurized milk does not increase in acidity during the first twenty-four hours, and but little after forty-eight hours. Schloss milk, which is very prone to induce scurvy, has a very low acidity. Evidently the answer does not lie in this direction. It is probable that pasteurized milk constitutes quite a different medium for the growth of bacteria than raw milk, and that it may favor the development of gas-forming or other types of bacteria.

In view of the fact that it has been stated by Braddon and Cooper,[6] in connection with beriberi, that there is a definite relationship between the amount of carbohydrate in the diet and the

occurrence of this disorder, for example, that when the carbohydrate is doubled, the rate of onset of beriberi is increased proportionately, it seemed worth while to observe whether this relationship obtained for scurvy. Accordingly, 3 per cent. of flour was added to the diet of four infants who were receiving the usual mixture of freshly pasteurized milk and barley water. In this way a milk food was prepared similar to some of the commonly used proprietary foods.[7] No noticeable effect was observed—certainly no result which could be interpreted as indicating the existence of a biologic law such as Braddon and Cooper have formulated for beriberi, which presupposes that carbohydrate requires a proportionate amount of "vitamin" for its metabolism in the body. On the other hand, the proprietary foods, composed of carbohydrates, which are stale and have been subjected to a high degree of heat, do seem to lead to scurvy.

TABLE I.—ACIDITY OF THE VARIOUS MILK PREPARATIONS USED

Type of milk.	Age. hours.	Number of cubic centimeters of tenth-normal sodium hydroxid required to neutralize 100 c.c. milk.							
		April 13	April 14	April 16	April 17	April 18	April 19	April 20	April 21
Raw	Fresh	14.9	14.1	16.9	18	18	17	17	18
Sterilized	Fresh	15.1	14.2	16.3	16	16	19	18	19
Sterilized (III)	48	16.0	16.4	16.5	23	21	21	23	20
Pasteurized (I)	Fresh	17.3	15.3	17.9	18	18	19	16	18
Pasteurized (II)	24	17.5	15.7	17.3	17	17	18	18	20
Pasteurized (III)	48	20.1	17.3	17.7	19	20	20	18	22
Pasteurized (III)	72*	16.6	23.2	17.0	18	27	19	21	24
Pasteurized (II) with flour†	24	....	....	....	..	13	13	14	16
Pasteurized (III) with flour†	48	....	....	....	13	36	14	19	16
Evaporated milk	24	....	....	....	..	..	29	21	21
Schloss milk	Fresh	8.4	6.4	8.7	6	7	7	6	12
Albumin milk	Fresh	26.4	28.6	41.4	40	46	34	39	49

* Last bottle of pasteurized III formula given on the following morning.
† Formula of two-thirds milk, one-third barley water, with 3 per cent. cane sugar.

From the foregoing it would seem clear that the preparation and condition of the milk may lead to the development of infantile scurvy. It is equally evident, however, that the milk cannot be the sole or determining etiologic factor. The mere fact that only a

few of the infants developed signs of this disorder under the various dietaries is convincing evidence of the participation of one or more additional causative agents. There is, indeed, no dietary of which it can be stated that it is certain to produce scurvy, no single food preparation of which we can postulate that, provided it is taken for a sufficiently long period of time, scurvy will certainly manifest itself. The nearest approach to this situation occurs when Keller's "malt soup" is fed to infants. It can be confidently stated that if infants are fed with this mixture of malt, flour, milk, potassium carbonate and water for five to six months, especially if pasteurized milk is used, the majority will evince definite signs of scurvy. Greatly to our surprise, we experienced this result a few years ago while we were using pasteurized milk. The fact that the disorder comes about more readily when pasteurized milk is employed, gives weight to the opinion of Neumann that the heating of milk for a second time lends it scorbutic qualities. We wish, however, to qualify his statement by adding that this seems to be true only if there is an interval between the two heating processes. If one pasteurizes the milk, allows it to cool, and then immediately brings it to the boiling-point, the twofold heating does not produce the same deleterious effect.

As is well known, scurvy, infantile scurvy, beriberi, pellagra, rickets, and some other diseases, have been linked together into one group; it is evident that there are symptomatic and pathological similarities among these diseases sufficient to render it profitable to group them together. In recent papers we have drawn attention to common symptoms in infantile scurvy and beriberi, such as cardiac enlargement and tachycardia, and others have brought out points of resemblance between members of this group. The basis of the classification, however, is etiological rather than symptomatic, and is founded on the assumption that they all are nutritional or rather dietary diseases. Although there has been an increasing tendency to admit their similarity and even their dietary nature, two totally different conceptions of their pathogenesis are current. One school regards them purely as "deficiency diseases," whereas the other believes that they are of toxic origin. Some twenty years ago Eijkmann,[8] in a paper which has become

classic, described a polyneuritis which he was able to produce in fowl and which closely resembled the beriberi of man. He attributed this disorder to a toxin found in the intestinal canal, and many subsequent investigators, repeating or enlarging on his experiments, expressed themselves of the same mind. Kohlbruegge[9] was the first, however, to suggest a grouping of these diseases, designating them by the name of "fermentative diseases" and asserting that they were due to poisons which were formed by harmful bacteria which had gained predominance in the intestinal canal. Very recently Williams,[10] after many years of work in this field, has also come to the conclusion that this group of diseases is of toxic origin. On the other hand, an entirely different conception has been in vogue for the past few years, mainly due to the writings of Funk.[11] This conceives of these disorders as being due entirely to a lack of essential food substances, the "vitamins"—as being essentially deficiency diseases. A division of opinion similar to that which exists regarding the etiology of this entire group of diseases, and as to beriberi in particular, exists in regard to the pathogenesis of infantile scurvy. Barlow took the point of view that it was brought about by a diet which had been deprived of some of its essential constituents. The excellent report of the American Pediatric Society[12] cautiously refrained from expressing a decided opinion on this point, merely declaring that "the development of the disease follows in each case the prolonged employment of some diet, unsuitable to the individual child." An interesting minority report of this committee signed by Caillé, however, rendered the opinion that it is "chronic ptomain poisoning due to the absorption of toxins." Neumann,[3] one of the most thoughtful observers and students of infantile scurvy, also regarded it as "a chronic poisoning." Hart,[13] who drew his conclusions mainly from experiments on monkeys, characterizes it as a "dyspeptic intoxication." Nevertheless, the literature contains many articles which accept Funk's point of view in its entirety and agree that we are dealing with a pure "deficiency disease."

A feature which has forced itself on the attention of many who have written on the subject is the multiplicity and variety of the foods which may bring about scurvy in the infant. Pasteurized

milk, milk containing a high fat percentage, buttermilk containing but little fat, albumen milk containing much protein, and the proprietary foods rich in starches, are among the varied and incongruous number. It is, of course, possible that these dietaries, however different they may seem, may all be lacking a common chemical constituent. What tends strongly against this point of view is the fact, already mentioned, that with none of these dietaries can scurvy be brought about with regularity. This lack of reaction between cause and effect must lead us to conclude that the deficiency cannot be the sole cause; indeed, that it does not act directly in bringing about the disorder.

In order to gain a clearer idea as to the possible nature of the etiological factors, it will be well to turn back and consider the nature of the symptoms and pathological changes of infantile scurvy. In the first place it should be remembered that we have signs of nerve involvement. These comprise cardiorespiratory phenomena, clearly indicating involvement of the pneumogastric nerves, occasionally changes visible in the optic disks, abnormalities of the deep reflexes, and probably sensory disturbances. The symptoms and changes common to this group of diseases, therefore, resemble those brought about by poisons of various kinds—the cottonseed poisoning in swine,[14] the toxic products of the wheat embryo,[15] or even mineral poisons, such as mercurial poisoning in man.[16] The nervous symptoms, especially the irritability of the heart, may be compared to those of the enterogenous intoxication or enterotoxic polyneuritis described by von Noorden.[17] The experiments of Abderhalden and Lampé[18] lend weight to the view of the formation of a toxin in the intestinal tract in this disorder. These investigators were able to bring about polyneuritis in pigeons and hogs by means of a restricted diet, and to cure the animals promptly by means of catharsis, castor oil or magnesium sulphate. They were led to attempt a cure by this means as they had noted that the polyneuritic pigeons passed very little stool and that the intestines at necropsy were markedly overfilled. They concluded that, particularly in the pig, toxic products are formed in the intestine. These novel experiments gain additional interest in view of similar results reported by McCollum[19] in connection with the scurvy of guinea-pigs. It

may be inquired as to the condition of intestines in infantile scurvy. When we search the necropsy protocols for lesions of the intestinal tract we find that in most cases there are merely occasional hemorrhages and swelling of the follicles and of the neighboring mesenteric glands. In some cases there is inflammation or ulceration of the colon.[20]

If a toxin is to be regarded as the proximate cause of infantile scurvy, the question naturally arises as to the nature of the toxin.[21] Is it exogenous or endogenous? There are some sound reasons for believing that the poison generally is not introduced preformed in the food. In the first place, infantile scurvy frequently develops in babies who are given milk of the very best grade; indeed, in contradistinction to rickets, it is not preëminently a disease of the poor. Furthermore, there is no relation between the concentration of the food mixture and its liability to induce scurvy. If, among a large number of infants receiving pasteurized milk from a common source, some are given milk diluted by one-half, others given it diluted by one-third, and still others whole milk, the last group will not show a preponderating tendency to scurvy, as we should expect were the poison contained in the food. Nor is it at all uncommon to encounter scurvy in an infant which has been fed with a very dilute milk mixture. The other side of this question, however, cannot be entirely dismissed. We should bear in mind that stale pasteurized milk is more apt to produce scurvy than freshly pasteurized, a fact which might be interpreted as in favor of an exogenous toxin. Again, the reports of the scurvy of adults being occasioned by decomposed food, as in Nansen's polar expedition and as reported on ships so frequently in the past, cannot be disregarded, and seem open to the interpretation as due, in part at least, to food poisoning. The experiments of Jackson and Harley,[22] who produced scurvy in monkeys by feeding them with tainted tinned meat, would seem to fortify this interpretation. But, as we have said, infantile scurvy develops in the overwhelming majority of cases on food which is not decomposed, so that, although we acknowledge the occasional role of exogenous poisons, we believe that the toxin is usually elaborated within the human body. As is well known, toxins are continually being formed in the intestinal canal by

bacterial growth. We are protected from the deleterious action partly by the counteraction of neutralizing bacteria. Should this protective force fail, the toxins may gain access to the tissues of the body. This is what happens in infantile scurvy. Whether the toxins differ in kind from those normally present in the intestine, or whether they are always the same, it is impossible to say. The various types of scurvy, as well as of rickets and of beriberi, may be due to differences in this regard.

According to this view, infantile scurvy is essentially a scorbutic auto-intoxication or intestinal intoxication; the diet is faulty in not being capable of inhibiting the elaboration of the poison. This raises the question, which must be left open for discussion, as to whether, from an etiological point of view, infantile scurvy should be regarded as an entity, or whether its symptoms cannot be produced by various poisons, some exogenous and others endogenous, formed as the result of an unbalanced flora in the intestinal canal.

If we consider scurvy an intestinal intoxication, we naturally inquire as to the functioning of the bowels in this disorder. This has been frequently discussed by writers on this subject, but a consensus of opinion is not apparent. Of the cases reported by the American Pediatric Society the bowels were regular in seventy-four instances, irregular in fifteen, constipated in 126, and diarrheal in seventy-seven. This question has assumed additional interest in view of recent experimental work on animals. As has been stated, Abderhalden and Lampé,[18] as well as McCollum,[19] found marked constipation in the course of their experiments. The latter expressed his conclusions in these words: "Scurvy in guinea-pigs is the result of retention of feces. I do not know whether or not the same is true of human scurvy."

Of course, there can be no question as to whether retention of feces by itself can bring about scurvy in infants; this is excluded by the marked instances of constipation frequently encountered among thriving babies. The majority of bottle-fed babies and a large number of the breast fed suffer from a greater or less degree of constipation. On looking up our records of infantile scurvy from this point of view, and comparing them with non-scorbutic infants, we have not been able to note a characteristic distinction. Some

of the infants which developed scurvy had normal stools as far as gross examination disclosed, others suffered from constipation, while a greater number showed a record of occasional loose stools. In reviewing the cases reported by others it would seem that, as in the report of the American Pediatric Society, this same lack of uniformity is manifest, but that in the advanced cases the stools are more often diarrheal. In this connection we must bear in mind that the malt soup preparation, the diet which, in our experience, has been associated with scurvy most frequently, is essentially laxative and almost never induces constipation. And, on the other hand, the most potent antiscorbutic both for adults and for infants, one which is effective at times when fruit juices have proved unavailing, is potato, a food which has no distinct laxative properties. It may be added, as noted elsewhere, that scurvy was found to develop in infants in spite of their receiving cod-liver oil or olive oil for long periods. We do not wish to conclude that the retention of feces is a negligible factor in the scurvy of infants, but rather that its role is quite secondary. When we assume that a poison is contained in the intestinal canal, it is evident that catharsis will be of value, and that constipation will aid in its absorption. This is true of all poisoning which occurs by way of the alimentary canal; for example, in lead poisoning, where catharsis has always been granted a distinct therapeutic place. It is probable that marked constipation may be assigned as one of the causes for the frequent occurrence of scurvy and allied intestinal intoxications among the insane, who neglect their bodily functions.

We have said that the value of potato cannot be ascribed to laxative properties. The same is true of orange juice, which is very mildly laxative, and cannot be depended on to relieve constipation in infants. Its therapeutic value in scurvy is probably due to its influence on the flora of the intestine and to its diuretic effect.

It is surprising that attention has not been called to the fact that *there is a diminished excretion of urine in infantile scurvy.* We have frequently observed this phenomenon, and its occurrence has been noted by the nurses. This oliguria is interesting from several points of view. It accounts in part for the edema which is so frequently met with in this disorder, and is of especial interest in connection

with the relation of body weight to infantile scurvy. Before noting this disturbance of metabolism we were at a loss to interpret the paradoxical phenomena of a scorbutic infant which was given orange juice being greatly improved and consuming considerable more food, but nevertheless failing to gain, or even reacting with a loss of weight. It was only when it was noted that the orange juice brought about a sudden outpouring of urine that the explanation was evident. Whereas before orange juice was given a baby urinated but three or four times a day, passing but 4 to 6 ounces of urine, thereafter it urinated fifteen to twenty times a day and passed 20 to 30 ounces of urine. A chart illustrating this condition is appended. It is probable that the citric acid of the orange juice induces the diuretic action. We had at various times tested the curative value of citric acid, considered by Netter[23] to be the essential deficiency of infantile scurvy, but, although we were able to bring about diuresis and to alleviate the symptoms temporarily, we were never able to effect a complete or permanent cure. In this connection we wish to call attention to the fact, mentioned also by Abderhalden and Lampé, that Funk's vitamins are claimed to belong to the pyridin and pyramidin groups, which possess diuretic properties. It is probable that the kidneys play a considerable role in infantile scurvy, its clinical course depending to some extent on the activity of their function, and that toxins are eliminated at an early stage by this route. This statement seems warranted in view of the frequency of urinary symptoms in scurvy—casts and blood cells in the urine, and the signs of parenchymatous inflammation which the kidneys may show at necropsy.[24]

Renewed interest has been awakened in the study of scurvy since it has become possible to reproduce the disease in animals. The first experimental work of this kind is generally associated with the names of Holst[25] and his co-workers, who induced scurvy in guinea-pigs by means of a diet of cereal grains. It should be noted, however, that the same result had been accomplished some years previously in this country by Theobald Smith.[26] During the past few years Baumann and Howard[27] have carried out the first metabolism investigations on scorbutic guinea-pigs. Although this work on animals has increased our knowledge considerably and is

certain to open new paths of investigation, caution should be exercised in transferring the results to human beings. The fact that we are able to produce scurvy in guinea-pigs by means of raw milk, a diet which effects a cure in infants, is evidence that some of the underlying conditions are different. An elaborate investigation on guinea-pig scurvy has recently appeared comprising papers by Jackson and Moody[28] and Jackson and Moore,[29] one entitled "Studies on Experimental Scurvy in Guinea-pigs," the other "Bacteriologic Studies on Experimental Scurvy in Guinea-pigs." The latter article is of especial interest, as it suggests tentatively that scurvy may be a bacterial infection. These investigators cultivated a diplococcus from the tissues of scorbutic animals after death, reproduced hemorrhages by inoculating cultures of these microörganisms into the circulation, and recovered the bacteria from the tissues some weeks later. This conception of scurvy as an infectious disease has been brought forward from time to time, especially in relation to epidemics of adult scurvy. Some years ago Ausset[30] claimed to have isolated "a pasteurella type of organism" from a case of infantile scurvy, and suggested that it was the causative agent of this disease. On the other hand, Hart,[31] Rehn,[32] Hirschsprung,[33] von Starck,[34] and Schmorl[35] have failed to find bacteria in the blood, although the total number of cultures seems to have been small. Czerny[36] reports negative growth from fluid aspirated from affected joints. Jackson and Moody's results, while most interesting, are open to the criticism that bacteria were found only after death, and that all blood cultures proved negative. This is, as stated, the same experience as has been encountered in infants.

One of the most striking clinical phenomena of infantile scurvy is the marked susceptibility to infection which it entails—the frequent attacks of "grippe," the widespread occurrence of nasal diphtheria, the furunculosis of the skin, the danger of pneumonia in advanced cases. Whether this is to be in part attributed to the disturbance in water metabolism, in view of the fact that a similar susceptibility exists in *Mehlnärschaden* cases, where the tissues likewise contain an excess of water, there is no basis for judging, but the clinical fact is striking and significant.

It is as one of these secondary infections, we believe, that the

findings in the guinea-pigs are to be interpreted. In this connection it is well once more to emphasize that when we refer to scurvy we do not regard it as a disease characterized by hemorrhages, but as a nutritional disorder which exists for months before the subperiosteal or other hemorrhages develop. This nutritional disorder, this simple scurvy, is not attributable to a bacterial invasion, although it leads to and is responsible for its occurrence. From the same point of view orange juice and other antiscorbutics are to be considered as of prime value in combating the toxic nutritional disturbance, but of no direct value in doing away with those hemorrhages which are brought about by bacterial infection. A hemorrhage of infectious origin, in contradistinction to those of toxic origin, must be regarded simply as a focal complication. The clinical course of many of these effusions, receding spontaneously or developing as the scorbutic condition improves, shows that they have local and not general significance. It is highly important that blood cultures should be carried out in the course of scurvy, and that particular attention should be paid to the stage of the disorder in which they are made.

Scurvy sometimes occurs in epidemic form. A few years ago we had the opportunity of observing an epidemic of infantile scurvy in connection with an outbreak of "grippe" at the infant asylum. We do not suggest this as a distinct type of this disease, for, as we have just said, infection is common as a secondary stage of scurvy. At times, however, when infection is widespread and scorbutic malnutrition exists among a group of infants, a considerable number of them may become infected and develop a hemorrhagic form of scurvy. It is an outbreak of this kind which we wish to describe in detail.

In February twelve infants in one ward developed fever and soon showed symptoms of various infections: otitis, pneumonia, nephritis, adenitis, etc. Three died of pneumonia; of the 9 who recovered, 7 suffered from what we shall term infectious scurvy, meaning by this a type of the disorder brought about by superimposing a secondary infection on the primary nutritional disturbance. Some of the infants showed signs of alimentary intoxication; most of them had no fever at the time the hemorrhages occurred, although they

may have had a rise of temperature when the infection began. In April a second epidemic of "grippe" took place and three more infants developed scurvy. The signs were mainly hemorrhagic, developing at sites both atypical and typical for scurvy. They occurred as follows: Case 1, left diaphysis of humerus and tibia; face; anterior abdominal wall at site of serum injection; right eyelid. Case 2, abdominal wall; cranium; vertebral column; external ear. Case 3, diaphysis of left femur. Case 4, cranial bones and external ear. Case 5, external ear and face. Case 6, diaphysis of tibia. Case 7, abdomen (Table II). These infants were receiving formulas made from milk pasteurized at 160° F. for twenty-minutes.

TABLE II.—DATA OF EPIDEMIC OF SCURVY

Case.	Age, mos.	Weight.	Site of hemorrhages.	Date.	Diet.	Remarks.
		Lbs. Oz.				
1. J. H.	6½	9 6	Humerus, tibia, face	Apr. 19	Breast milk (1 week); breast milk, buttermilk and orange juice	Grippe since end of February; nephritis; v. Pirquet negative.
		10 4	Upper eyelid	May 9		
2. L. S.	5	12 14	External ear, parietal bones, vertebral column, abdominal wall	May 4	Pasteurized milk formula; orange juice 1 oz. daily since April 22	Twitchings and convulsions; signs of intoxication; red blood cells in urine; fever to 101° F.; v. Pirquet negative.
3. A. R.	10	12 8	Femur	Apr. 19	Pasteurized milk formula; vegetables for a month; orange juice longer; getting orange juice and vegetables	Grippe end of January; again in April; fever until April 17; v. Pirquet positive; gums negative.
			Femur again swollen and tender	June 4		
4. D. E.	5	7	Both ears; parietal bones	Apr. 29	Breast milk since April 19; May 30 changed to pasteurized milk	Grippe throughout March; intoxication; nephritis; no relapse although no orange juice given.
5. T. K.	10	15 13	Ear and face	Apr. 27	Pasteurized milk, cereal, vegetable, soup; orange juice since April 15	Two teeth; gums negative; v. Pirquet negative.
6. P. G.	4	8 4	Tibia	May 8	Pasteurized milk formula	Grippe end of February and first half of March; gained 20 oz. during last month; v. Pirquet negative.
7. I. P.	2	6 4	Abdomen	Mar. 7	Breast milk for past week	Grippe; probable source of epidemic.

It is striking that many of the hemorrhagic signs above outlined are quite different from those encountered in infantile scurvy. We

have never met with such widespread subcutaneous hemorrhages, and have noted them in the literature only in the most advanced cases. But what makes these cases stand out sharply from ordinary scurvy is not so much their exceptional symptomatology as their lack of response to specific therapy. Two had received breast milk for two weeks previous to the onset of symptoms; one an ounce of orange juice for two weeks; one an ounce of orange juice and also vegetable for two months previously; one vegetable and orange for a week; and another vegetable for an indefinite period before the onset. One baby, aged nine months, who had a tender swelling of the diaphysis of the femur in April, had a relapse of symptoms in June in spite of having received orange juice and vegetables throughout the intervening period. It should be noted that of the seven infants four were under six months of age, which, from a practical standpoint, and although subject to exceptions, is rightly regarded as the minimum age for the hemorrhagic stage of this disorder. Again, although two babies had teeth, neither showed spongy gums nor peridental hemorrhage. The swellings of the long bones, however, were quite typical of the subperiosteal hemorrhages of infantile scurvy, and are open to no other clinical diagnosis.

How are we to interpret this picture? The ages of the infants, the distribution of the hemorrhages, the development of signs in some cases in spite of antiscorbutic diet, the sharply defined epidemic character of the disease, distinguish it from the scurvy we commonly meet with. We believe that the epidemic was brought about by a bacterial invasion. Whereas usually scorbutic intoxication must be prolonged for a period of about six months to allow the secondary invasion of bacteria, in this instance, due probably to the peculiar nature of the bacteria, invasion occurred early and in some infants which were receiving an antiscorbutic diet. In most of these instances, however, it should be noted that the infants had been receiving pasteurized milk for months, and the antiscorbutic foodstuff had been added but a few weeks previously. Latent scurvy was prematurely changed to florid scurvy by the presence of a ward infection; an epidemic of "grippe" precipitated an epidemic of scurvy exceptional in its hemorrhagic tendency.

In closing we may add that this epidemic resembles the epidemics

of melena neonatorum which occur from time to time in lying-in hospitals and which formerly visited these institutions so frequently. Not long ago we had the opportunity of observing an epidemic of this character where, within a few weeks, some eighteen new-born infants developed hemorrhages at various sites—the umbilical cord, mouth, nose, skin, etc. These cases must also be considered bacterial in nature. Finally, we wish to suggest that many of the reported instances of scurvy in breast-fed babies are to be regarded as cases of sepsis grafted on general malnutrition due to syphilis, tuberculosis and undernourishment, rather than as true scurvy.

Conclusions. One of the several factors in the pathogenesis of infantile scurvy is faulty diet. Pasteurized milk was found to be a contributing cause if it was not fresh—if given twenty-four to forty-eight hours after pasteurization. From this point of view milk pasteurized in the city is preferable to milk pasteurized at the creamery, which reaches the consumer much longer after the heating process. Aging seemed to play a greater role in the production of scurvy than heating, whether the milk was pasteurized or raised to the boiling-point. It was found that even raw milk on aging loses its antiscorbutic properties.

Infantile scurvy is not, however, a simple dietary disease. The diet is at fault in allowing the intestinal bacteria to elaborate toxins. It is doubtful whether the toxin is always the same, and therefore whether, from a strictly etiological standpoint, this disorder should be regarded as an entity. Infantile scurvy is an intestinal intoxication or an auto-intoxication due to the overgrowth of harmful bacteria in the intestine. It is the product of an unbalanced flora which is no longer controlled by a proper dietary.

Oliguria is a common symptom of scurvy. The mild therapeutic effect of citric acid may be ascribed partly to its diuretic properties. Orange juice also was found to bring about marked diuresis.

One of the striking and important symptoms of scurvy is a susceptibility to infection (furunculosis, nasal diphtheria, "grippe," etc.). Some hemorrhages are due to this secondary infection, and are to be regarded not as scorbutic, but rather as focal complications. Other hemorrhages are truly scorbutic. Scurvy, however, is essentially a disorder characterized by malnutrition and not by

hemorrhage, taking months to develop, and, from a clinical point of view, frequently latent or subacute.

Infantile scurvy occurring in epidemic form is described. This results when latent scurvy exists among a number of infants and an infectious disease (such as "grippe") is superadded.

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2. In the article[1] referred to above on "Subacute and Latent Infantile Scurvy" this point was brought out as follows: "In referring to pasteurized milk as inducing scurvy I do not wish to state that the heating is necessarily altogether responsible for the result. There may well be other contributory factors, such as the staleness of the milk."

3. Neumann, H.: Deutsch. Klin., 1904, vii, 341.

4. We found that as a matter of fact the interval following pasteurization was forty-eight hours in milk which we received and which had been pasteurized at the creamery. The milk was stored by the dealers for twenty-four hours in the city, so as to provide a constant supply in case of delay or failure of delivery from the country.

5. Variot, G.: Compt. rend. de l'Acad. d. sc., 1905, cxxxix, 1002.

6. Braddon, W. L., and Cooper, E. A.: Brit. Med. Jour., June 20, 1915.

7. The flour was cooked with the barley water and sugar and added to the pasteurized milk.

8. Eijkmann, C.: Virchows Arch. f. path. Anat., 1897, 253.

9. Kohlbruegge, J.: Centralbl. f. Bakteriol., Orig., 1911, lx, 223.

10. Williams, R. R.: Am. Med., November, 1916, 756.

11. Funk, C.: Die Vitamine. J. F. Bergmann, Wiesbaden, 1914.

12. Rep. Am. Pediatric Soc.: Arch. Pediat., July, 1898, 481.

13. Hart, C.: Jahrb. f. Kinderh., 1912, lxxvi, 507.

14. Rommel and Vedder, E.: Jour. Agric. Research, 1915, v, 489.

15. Hart, E. B., and McCollum, E. V.: Jour. Biol. Chem., 1914, xix, 373.

16. In chronic mercurial poisoning the following suggestive symptoms occur: Anemia, bleeding and spongy gums, loosening of the teeth, a quickened pulse, ulcers of the extremities. At times mercury attacks the nervous system, producing palsy. The resemblance is heightened by the fact that calcium metastases have been found in the muscles in experimental scurvy (Hart) comparable to those characteristic of mercurial poisoning.

17. von Noorden, C.: Berl. klin. Wchnschr., 1913, l, 51.

18. Abderhalden, E., and Lampé, A. E.: Ztschr. f. d. ges. Exper. Med., 1913, i, 296.

19. McCollum, E. V.: Jour. Am. Med. Assn., 1917, lxviii, 1381.

20. There is one lesion in the intestinal tract to which we would call attention, as it was present in a necropsy performed a few years ago and has been recorded by others —a marked injection of the mucous membrane of the first part of the duodenum. Additional significance would seem to be attached to this lesion in view of the fact that it is noted in some necropsy protocols in cases of beriberi and of pellagra. It may well be that this inflammation is the result of products excreted by the liver and poured into the intestine at this point.

21. There are probably many factors which influence the occurrence of scurvy. Certainly climate plays a role. We have frequently found that scorbutic symptoms will disappear when infants are placed out of doors and exposed to the sun and air in the spring months. Scurvy is more prevalent in the winter, as is rickets. No doubt general nutritional diseases act as predisposing factors, among which rickets and syphilis are important.

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SERUM TREATMENT OF LOBAR PNEUMONIA

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This report deals especially with cases which were diagnosed clinically, bacteriologically and by postmortem as lobar pneumonia due to the pneumococcus. Reference is made to cases which were given antipneumococcus serum but which at autopsy were shown not to be lobar consolidation. There are added also cases of infection with streptococcus hemolyticus, but these are included by way of contrast only, our conclusion being that cases of pneumococcus infection present clinical features quite different from those of streptococcus infection. Streptococcus may be, and frequently is, superimposed upon the pneumococcus or may occur separately. Whether separate or in conjunction with the pneumococcus, we believe that the clinical features are differentiable in the majority of cases.

We have looked upon the mixed infections as similar to the complicating infection of pyogenic organisms in typhoid or smallpox. Moreover, we have felt that bronchopneumonia should not be considered as having anything to do with lobar pneumonia any more than the tuberculous ulcer of the intestine should be considered in connection with typhoid ulcer except to show the difference. The pneumococcus infection of whatever type when treated at the outset with serum, in our experience, does well. When treated late it assumes all the serious features with which we were familiar before serum was used, when the mortality ranged from 20 to 50 per cent. From bacteriological findings we have concluded that those cases which were treated late became, through the action of the pneumococcus, fertile

soil for other pyogenic organisms or at least reduced the resistance to such an extent that other pyogenic organisms found non-resistant soil in which to flourish. We have been unable to demonstrate whether these pyogenic organisms were previously lodged in the individual, in the throat, for example, or whether they gained access during the pneumococcus infection. We have on meager evidence inclined to the former. The serious pulmonary sequel to measles, which is so fatal in military hospitals, we have considered as a disease distinct and separate from the pneumococcus lobar pneumonia. In our experience the pneumococcus has been an extremely rare complicating infection in measles. I will not consider further this pulmonary complication of measles, for it is so different clinically, anatomically and bacteriologically that it belongs to a separate discussion. The report of "pneumonia" as a complication or cause of death in measles should be abandoned as incorrect and misleading. The Surgeon-General's Office has adopted the term "measles pneumonia," but we believe that the term "pneumonia" should not be used at all in this connection.

From the statistics of the Rockefeller Hospital and from the review of our 139 cases, we feel that the pneumococcus pneumonia when treated with the serum early is a comparatively mild infection. I would like to repeat that this report deals with those cases which show, clinically, consolidation of part or of an entire lobe of the lung and due to the pneumococcus.

SUMMARY OF CASES

I. Pneumococcus Alone

Type uncomplicated.	Incidence.	Recoveries.	Deaths.	Mortality. Per cent.
Type 1	26	25	1	3.8
Type 2	18	17	1	5.5
Type 3	10	10	0	0.0
Type 4	27	27	0	0.0
Total	81	79	2	2.4

It is noteworthy that the two fatal cases were colored and both worked as stevedores. Nephritis complicated the pneumonia in both cases, the one of chronic type, the other an acute nephritis developing during the height of the disease. Each received large

doses of serum on and after the fifth day of the disease. At necropsy each showed characteristic lobar consolidation and evidence of nephritis in addition.

	Incidence.	Recoveries.	Deaths.	Mortality. Per cent.
II. Pneumococcus and Streptococcus				
Type 1	3	2	1	33.0
Type 2	0	0	0	0.0
Type 3	0	0	0	0.0
Type 4	2	1	1	50.0
Total	5	3	2	40.0
III. Streptococcus Alone (Hemolyticus or Viridans)	11	5	6	54.0
IV. Undetermined (Not Pneumococcus or Streptococcus)	39	38	1	2.2
V. Miscellaneous.				
Pneumo Type 1 and 2	1	1	0	0.0
B. influenza	1	1	0	0.0
Staphylococcus in throat	1	1	0	0.0
Grand total	139	128	11	7.9

Method of Procedure. Immediately upon the finding of clinical signs indicating an area of consolidation, the patient is desensitized with polyvalent antipneumococcus serum (Mulford's) and placed in a pneumonia ward, where the following instructions are posted and strictly adhered to:

Instructions—Medical Service

Instructions to the medical staff regarding all cases of lobar pneumonia

"1. Isolation: Caps, gowns and gauze mouth guards for attendants, nurses and doctors. Sheets between beds and mouth guards for patients leaving bed.

2. Sputum: (*a*) Collect sputum in sterile bottles and send to the pathologist at the clinical laboratory for transmission to the department laboratory. (*b*) Laboratory slip marked as follows must

accompany the sputum: 'Sputum for determination of pneumococcus type.' (*c*) The specimen must reach the department laboratory within four hours after it has been expectorated.

3. Urine: Collect 6 ounces of the twenty-four hours' specimen in a sterile bottle and send to the pathologist at the clinical laboratory for transmission to the department laboratory. A laboratory slip marked as follows must accompany the specimen: 'Urine for Pneumococcus Differentiation.'

INSTRUCTIONS FOR SUCH CASES OF LOBAR PNEUMONIA AS ARE TO RECEIVE SERUM TREATMENT

Desensitizing: (*a*) Administer 2 c.c. of serum subcutaneously and at two hours' interval administer the following amounts: 3 c.c. and 5 c.c., a total of 10 c.c. After each administration look for signs of hypersensitiveness, such as: (1) Difficulty in respiration. (2) Cyanosis. (3) Violent coughing. (4) Sense of restriction about chest. (5) Marked variation in pulse. In case these occur give same dose as previous one at the end of two hours' interval. (*b*) From two to four hours after the last desensitizing dose, administer the balance of the 100 c.c. intravenously. (*c*) Administer 100 c.c. intravenously every twelve hours. The intravenous administration of serum, warmed to body heat, should be given by gravity, and very slowly. In case signs of hypersensitiveness, as noted above, occur during the administration of serum, stop the serum at once.

Serum Sickness. This is not a serious condition and does not contraindicate the continued administration of serum, though it is due to the serum.

The manifestations are fever, itching and redness of skin, urticaria. This condition is entirely different from true anaphylaxis, which in mild form would be manifested by the symptoms of hypersensitiveness noted above and which in severe form may be rapidly fatal."

In the early part of the winter our laboratory facilities were inadequate and it required some time to get a report on the sputum from the department laboratory, four miles away. This inadequacy still (March, 1918) exists on account of the difficulty in procuring mice

and the need of a larger laboratory and staff of laboratory workers. The patients, however, did not suffer in consequence, as the polyvalent serums were administered without waiting for laboratory findings. If the report Type I was returned, the patient received Type I serum, otherwise the polyvalent serum was continued. The polyvalent serum used has been prepared according to Mulford, so as to prevent the neutralizing of the Type I element, so that in giving the polyvalent serum, Type I in full strength is being given, if Mulford's claim is correct. We have no proof of this beyond our clinical results. We believe too that by using the small doses to desensitize, the patient is better prepared for the larger doses and the danger of anaphylaxis is minimized. We have preferred the subcutaneous to the intradermal method, because with the varying personnel in a military hospital we consider it safer to desensitize than to attempt to ascertain the sensitiveness of the subject, with possible grave errors in judgment. Even with the trained observers at the Rockefeller Hospital such errors in judgment are reported by Cole.[1]

Clinical Features. The three striking features have been: (1) Variations in temperature; (2) The rapid recovery; (3) Absence of profound toxic effects.

The rapid breathing, flushed face and further manifestations of profound toxemia have been absent in the majority of our cases unless complicated by some other septic organism. A careful inspection of our temperature charts fails to reveal any uniformity of the lobar pneumonia curve. Invasion by another organism is usually accompanied by a greater variation in the curve, but a number of the cases in which no other organism could be demonstrated have shown a temperature decline with a step like lysis similar to that of typhoid but without the long typhoid period of decline. Extension of the pneumonic process or involvement of another lobe is marked by a sharper and more sustained rise, whereas invasion by another pyogenic organism presents a more gradual rise and shows greater variations. About 5 per cent. of the cases show the sustained temperature with the sharp critical fall commonly described as char-

[1] Ref. monograph Acute Lobar Pneumonia, Rockefeller Institute, No. 7, October 16, 1917, p. 63.

acteristic of the pneumonia curve. The leukocyte count, beyond indicating a good prognosis when high, has been no guide as to the development of complications or extension of the process.

Complications. Empyema and otitis media have been the most frequent. The former of these will be dealt with in a separate report. Two cases presented pneumococcus abscesses of the abdominal wall. Streptococcus pericarditis occurred in two cases. Mediastinal abscess in one case. Meningitis in one case only. This case will be described under the Fatal Cases. Acute nephritis occurred in about 15 per cent., as evidenced by albumin and casts in uncomplicated cases; 75 per cent. in complicated cases.

Serum Treatment. The amounts of serum administered have varied between 50 c.c. and 600 c.c., with an average of 250 c.c. About 10 per cent. of the cases did not require serum treatment. In the military service it is possible to begin the serum treatment much earlier than in civil practice. Few of our cases have come under treatment later than the third or fourth day, and many of them have been treated in the first forty-eight hours. Treatment was begun on the first clinical sign, without waiting for differentiation of type. For this purpose polyvalent serum was used. If the case showed Type I this serum was used, otherwise polyvalent serum was continued. No systematic blood cultures were made on our cases, but from the Rockefeller report[1] and from our low mortality we concluded that the early administration of serum prevented the development of or cleared the blood of pneumococcus organisms. In the few cases in which blood cultures were made this conclusion was supported. The rapid recovery of between 50 and 60 per cent. of all cases would indicate that the early use of serum tends to diminish the frequency of the complications.

Preventive Treatment. Dichloramin-T in chlorcosane 2 per cent. was used as a throat spray for attendants and with some of the cases. With the measles cases we found that pulmonary complications were less frequent when this treatment was employed.

Serum Sickness. About 50 per cent. of the cases showed signs of serum reaction. These ranged from simple erythema to the extensive

[1] Monographs of the Rockefeller Institute for Medical Research No. 7, October 16, 1917, p. 79.

urticaria, with general swelling and joint pains. Some of the severer cases developed after 50 c.c. of serum had been given and others showed no reaction after 400 to 600 c.c. Manifestations appeared from twelve hours to fourteen days after administration. Only 2 cases showed any alarming features. One of these had blood and blood casts and excessive amount of albumin in the urine. The other, who received only 50 c.c. of serum, with prompt fall of temperature, which remained normal, two weeks later developed general swelling, making him unrecognizable, together with swelling and pains of many of the large and small joints and with albumin and hyaline casts in the urine, all of which disappeared in five or six days. In some of the cases we have endeavored to determine whether a mononuclear increase in the blood would indicate a serum rise of temperature, as suggested by Cole, but we found no uniformity in this from which conclusions could be drawn.

Anaphylaxis. Only 1 case presented symptoms of anaphylaxis. This was a case of asthma of unknown cause. In desensitizing him he showed no reaction, but when 80 c.c. of serum had been administered, cyanosis, dyspnea with asthmatic breathing, cold sweat, disturbed, rapid heart action and general signs of collapse developed. Administration of serum was continued up to 100 c.c., and subcutaneous injection of adrenalin was given. In twelve hours the temperature was normal and continued so, requiring no further treatment.

Streptococcus Infection Alone and Complicating Pneumococcus. Reference to the Table will show the frequency of these conditions. We have not practised streptococcus vaccination. With the accumulation of evidence it is becoming more and more apparent that when this organism is added to pneumococcus infection the case assumes grave features. To combat this added infection we are preparing to carry out immunization with streptococcus vaccines. This measure has been resorted to in some of our base hospitals and is suggested by Cole and MacCallum in a recent communication.[1] The destructive power of the streptococcus is well demonstrated in the pulmonary complication of measles, in which the pneumococcus is rarely found. In reviewing the records one is disposed to conclude

[1] Jour. Am. Med. Assn., April 20, 1918, No. 16, lxx, 1151.

that it is the streptococcus, superimposed upon pneumococcus, that gives lobar pneumococcus pneumonia its real virulence. Early treatment with serum seems to lessen the tendency toward the development of this mixed infection. While slight tingling of the conjunctiva is common in this disease, we found marked jaundice of the conjunctiva in those cases of streptococcus infection alone or complicating pneumonia.

Other Treatment. Diet: While this is a comparatively brief febrile disease we have felt it advisable to maintain a diet of about 2000 calories, consisting of easily digested fluids and semisolids; 3000 c.c. or more of water a day is routinely given. Whisky has been given when indicated.

Heart Stimulants: We have in most cases followed the advice contained in the Rockefeller monograph, namely, digitalizing early. We have used Merck's digipuratum tablets, $1\frac{1}{2}$ grains each. One such tablet given three times a day for *three days*. Strychnin was not given.

Abdominal Distention: This has been an infrequent feature. In 3 of the cases peritonitis was suspected and was found at autopsy in 1 of these. By the use of oil and turpentine stupes, enemata and by the regulation of diet the distention was relieved in most cases.

Open Air: For the greater part of the winter, patients were moved to verandas and allowed to remain there from 11 A.M. to 4 P.M., protected by screens. (*Lobar cases only.*)

IMPORTANT POINTS. 1. Early diagnosis is essential.

2. Clinical signs of consolidation should be followed by immediate use of polyvalent or other serum.

3. If more than 250 c.c. of serum are required and the temperature and toxic signs continue, complication by other organism should be suspected; like malaria, when treated with quinin the pneumococcus is rapidly overcome by serum.

4. Uncomplicated pneumococcus infection is a comparatively harmless and rarely a fatal condition.

5. The colored men are more susceptible, possibly because they keep up and about longer and come under treatment late. Their complaints may be disregarded by officers who think them shirking.

6. Leukocytes are not a reliable guide in determining the added

streptococcus infection. Mononuclear increase is not a guide in determining serum temperature rise from septic temperature.

7. Protective streptococcus vaccination should be employed.

8. Diet: 2000 calories; 3000 c.c. of water should be administered daily.

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CHRONIC SEPTICEMIC ENDOCARDITIS WITH SPLENOMEGALY; TREATMENT BY SPLENECTOMY

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In the face of a disease like cancer or sarcoma we accept our helplessness with resignation, but we chafe against our helplessness in so-called malignant endocarditis, for we feel that we should be able to master it. It is an infective process, due to well-known bacteria which in other circumstances may be successfully combated. Dr. Libman, in his several admirable papers, has shown that patients suffering from this type of endocarditis may become bacteria-free and yet succumb to the disease. If death were an early event the failure of our efforts might be more easily understood, but the affection may last for months, or even for one or two years, so that ample time exists for treating it, and yet nearly every case terminates fatally.

I shall not go into detail regarding the symptoms of the affection, with which the writings of Osler, Dock and Libman have made us familiar. The outstanding features are fever of long duration, which may resemble that of tuberculosis or malaria; anemia of varying intensity, sometimes so severe as to suggest one of the primary anemias; pains in the joints; petechial spots on the skin and mucous membranes; heart murmur. Albuminuria is common and in later stages the signs of a true nephritis may appear. Abdominal pains, sometimes sudden in onset and suggesting embolic processes in the spleen or kidneys, are not infrequent. Cough and insomnia are often very troublesome. From the diagnostic point of view the heart murmur is the most important thing; it may be very faint or it may

be loud and distinct. I have seen cases with mitral, with aortic and with pulmonic lesions; on the whole, however, I have gotten the impression that the aortic cases are the most frequent. The affection nearly always attacks a valve previously diseased as the result either of rheumatism or of some allied condition, such as tonsillitis or chorea. It may, however, have its starting-point on an intact valve, as I have observed in gonorrhea and in one case of pneumonia, in which the pulmonic valve became involved. Such cases generally run a more acute course, with higher fever, and do not present so prominently the renal features. However, there is a primary chronic form of endocarditis which in its course and termination is indistinguishable from that in which the lesion is a secondary one upon a previously diseased valve.

One other feature is important, and that is the condition of the spleen. This organ is practically always enlarged, and in some cases so much enlarged that it may become the dominant feature to the point of completely obscuring the underlying heart affection. It is of this group of cases, those characterized by a true splenomegaly, that I wish especially to speak. The spleen may extend down to the level of the umbilicus, or even lower; it is smooth, rather firm, rarely tender, though often the seat of spontaneous pain. Such a striking enlargement may readily lead to a wrong diagnosis, especially to that of splenic anemia or Banti's disease. It is easy to see why such a diagnosis might be made. There is the prominent spleen, the profound anemia, at times a striking leukopenia; and if a murmur is found it will often be attributed to the anemia. Petechial hemorrhages, so valuable in the diagnosis, may be entirely absent throughout the long course of the disease.

I am inclined to think that not a few cases of so-called splenic anemia or Banti's disease treated by splenectomy were in reality cases of chronic septicemic endocarditis. The leukopenia in a disease in which one would expect leukocytosis might readily, though erroneously, tilt the diagnostic scale in favor of splenic anemia.

Watching a number of cases in the past two or three years and finding that neither autogenous nor stock vaccines, transfusions, drugs or other measures did aught to avert death, I began to wonder whether there was not some other factor besides the heart that was

of importance in the fatality of the disease. Baehr,[1] Löhlein,[2] Ophüls[3] and others have called attention to embolic processes in the kidney; they undoubtedly play an important role in the course of the disease. Yet we must not overlook the possible significance of the large spleen. The spleen is a filter for bacteria. Whether it kills them or only benumbs them, leaving their final execution to the liver, is not definitely known. Bacterial filtration is not a passive process, but according to Rosenow and to Ozaki[4] it is dependent upon vital activity of the cells, upon a selective action on their part, a bacteriotropism. The filtration causes an accumulation of bacteria in the spleen which leads to hypertrophy, a sort of work hypertrophy, as William Mayo calls it. Through the multiplication of bacteria, and perhaps through their subsequent autolysis, increased quantities of toxins are thrown into the circulation. Moreover, living bacteria are often present in old infarcts of the spleen, as shown by Ophüls.[5] In these ways an infectious disease may be kept up and perpetuated, although the primary focus is no longer existent or active. An example or two will serve to illustrate this point. In syphilis the spleen at times is greatly enlarged, and in such cases antisyphilitic treatment does little or no good, probably because the treponemas are well protected in the spleen pulp and tissues. Removal of the spleen brings about a cure, especially if it is followed by a course of antisyphilitic treatment. In chronic malaria the blood is often free from plasmodia, while the spleen shelters them in enormous numbers.

The long-continued existence of bacteria in the spleen in endocarditis may therefore be the principal reason why the so-called bacteria-free cases go on to a fatal termination. If we could get rid of the large disease-harboring focus represented by the spleen, it might be possible to deal with the bacteria present in the heart valves. Enough antibodies might be developed to destroy them, while so long as the spleen continues to pour toxins into the blood, the body, as we know only too well, can never make any headway.

[1] Am. Jour. Med. Sc., September, 1912, 327.
[2] Arbeit. aus dem path. Inst. zu Leipzig, 1907, No. 4.
[3] Jour. Am. Med. Assn., November 13, 1915 and October 13, 1917.
[4] Jour. Med. Research, July, 1917.
[5] Jour. Am. Med. Assn., November 13, 1915.

There is another factor to be considered: Enlargement of the spleen is brought about chiefly by a proliferation of cells to a lesser degree by an increased blood content. This proliferation, according to the theory of cellular toxemia which I proposed several years ago,[6] causes the pouring into the circulation of enormous quantities of metabolic products which have to be handled by the liver and other organs and tissues.

In view, therefore, of the hopelessness of our treatment of chronic septicemic endocarditis, and in view also of the value of splenectomy in other infectious diseases, as in syphilis, malaria and, if it be infectious, in splenic anemia, I believe we are warranted in removing the spleen if it is enlarged. In this connection it should be remembered that, as William Mayo[7] has pointed out, enlargement of the spleen may exist even though the organ cannot be palpated.

On the basis of these thoughts we undertook the operation in one case, and while the ultimate outcome was not all we had hoped, failure was due to an unusual complication which caused the patient's death some time after the operation.

The notes of the case are as follows:

I. F., a man, aged fifty-seven years, a patient of Dr. H. B. Shmookler, has been failing in health for a year. In the last four months he has had a more or less continued fever associated with joint-pains, but without joint swellings. His spleen has been enlarging, at first gradually, of late more rapidly. A profound anemia has coincidentally developed. From time to time there have been attacks of sharp pain in the left hypochondrium. At no time has he had any hemorrhage from the nose, mouth or bowel. Twelve years ago, following an injury to the head, he began to have epileptiform seizures of Jacksonian character, which later gave place to attacks of petit mal. When I saw the patient, October 31, 1917, I found him exceedingly pale and weak. The heart was somewhat enlarged and there was a systolic murmur at the mitral area transmitted into the axilla. This murmur I learned had existed for many years. Petechial spots were present over the legs. The most striking feature, however, was an enlarged spleen which extended to the level of the umbilicus. A blood examination gave the following results: Hemoglobin, 45 per cent.; red cells, 2,220,000;

[6] The Cellular Factor in Infectious Diseases, Jour. Am. Med. Assn., February 20, 1915.

[7] Mayo Clinic, 1916, v, cxi, 628.

white cells, 4800; polymorphonuclear cells, 82 per cent. Considering the case to be one of septicemic endocarditis, with splenomegaly, I advised removal of the spleen, preceded by transfusion. Two transfusions were done, the second, which was of appreciable benefit, on February 3, 1918. On February 5 the patient was admitted to the Lankenau Hospital, where an immediate blood count showed:

Hemoglobin, 40 per cent.
Red blood cells, 2,020,000.
White blood cells, 4450.
Polymorphonuclears, 80 per cent.
Lymphocytes, 6 per cent.
Large mononuclears, 8 per cent.
Transitionals, 6 per cent.
Eosinophiles, 0 per cent.

The urine examination gave the following result:

Color, yellow.
Reaction, acid.
Specific gravity, 1015.
Albumin, a faint trace.
Sugar, none.
Urea, 1 per cent.
Bile, 0.
Indican, 0.
Diacetic acid, 0.
Acetone, 0.
Many granular casts.
Epithelial cells.
White blood cells.

The phenolsulphonephthalein test resulted as follows:

First hour, 7 per cent.
Second hour, 12 per cent.
Third hour, 14 per cent., making a total of 33 per cent.

Blood urea: 66 mg. per 100 c.c. of blood.

On February 6 the spleen was removed by Dr. Deaver, under ether anesthesia. It was found to be enormously enlarged and adherent to the diaphragm at the upper pole. The spleen with blood weighed 1570 grams, without blood 1160 grams. The surface showed two scars, evidently the result of infarction.

Dr. Reimann, pathologist of the Lankenau Hospital, gave the following report on the microscopic examination:

"The spleen is not the spleen of Gaucher's disease, Banti's disease, malaria, tuberculosis, syphilis, Hodgkin's disease or the leukemias. There is endothelial hyperplasia, diffuse around the blood sinuses, just as in the ordinary acute splenic tumor. *e. g.*, typhoid. The inference is that the

patient has a long-standing infection of very low virulence or a long-standing toxemia."

The day following the operation the hemoglobin rose to 50 per cent., and the red cells to nearly 4,000,000 from 2,020,000. At the end of a month the hemoglobin was 55 per cent., and the red cells just under 3,000,000 and the leukocytes had risen to 6250, with 68 per cent. polymorphonuclears instead of 80 per cent.

On the ninth day the stitches were removed, but there was no healing and the patient eviscerated himself. The bowels were reduced and the wound closed under chloroform anesthesia. No infection ensued.

After the operation the patient improved amazingly in appearance; his hands were no longer cold and he lost the yellowish cachectic pallor which had been a striking feature. Both Dr. Deaver and Dr. Shmookler felt that the operation had justified itself by the improvement that followed.

On March 9 the patient began to have trouble with his larynx and extreme difficulty in breathing. Dr. Butler thought there was an abscess of the larynx. Treatment proved of no avail.

The man thus lived a month after the operation; notwithstanding the fact that he had eviscerated himself and had to have a second operation, his general condition as well as the blood showed a decided improvement; and while we do not know what would have happened had the laryngeal abscess not supervened, it is reasonable to suppose that the improvement would have continued.

I have brought this single case before you in the hope that the operation may be undertaken by others.

In conclusion, I want to say a word about the name of this disease. It has received many designations: Chronic septic endocarditis; malignant endocarditis; chronic infectious endocarditis; chronic ulcerative endocarditis; endocarditis lenta; subacute bacterial endocarditis. The most desirable designation would naturally be one based on the causative organism. Such a designation, however, is not sufficiently descriptive for practical purposes. Inasmuch as the most prominent feature of these cases is a long-continued septicemia, I feel that the phrase "chronic septicemic endocarditis" is probably at present the most satisfactory bedside diagnosis.

INVESTIGATION OF TRENCH FEVER IN NORTHERN FRANCE

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The disease trench fever as described in previous publications is so well known that we shall not take your time with a further description of it. Its presence in the British army was first called attention to by Graham.[1] Hunt, Rankin and others also published concerning it. McNee, Brunt and Renshaw,[2] in an excellent publication, described the disease and demonstrated by careful experiments its infectious nature. They transmitted it to healthy men by the intravenous or subcutaneous injection of blood taken from trench-fever patients during the active stage of the disease. They concluded that the disease was a definite entity and their experiments seemed to show that the virus was contained within the blood corpuscles themselves, whether leukocytes or red cells. Blood corpuscles after being washed five times in saline solution to remove the plasma were still found to be infectious. This observation, they state, has further supported their view that the virus is intracorpuscular. More recently, McNee[3] reported that the virus is found in the whole blood and is especially associated with the corpuscular elements and is not in the serum or plasma. Filtrates of the serum and of extracts of the corpuscles gave negative results after inoculation. In spite of McNee's careful work a number of observers have thought that trench fever might represent an obscure

[1] Lancet, September 25, 1915, ii, 703.
[2] British Medical Journal, February 12, 1916, i, 225.
[3] Medical Bulletin, American Red Cross, January, 1918.

form of typhoid or paratyphoid fever occurring in individuals partially immunized by inoculation.

On account of the great loss of man power caused by this disease among the armies in certain parts of the Allied Western Front, one of us concluded that the method of transmission of trench fever was an important problem for investigation in relation especially to the prevention of the disease. Through the Medical Research Committee of the American Red Cross, authority and funds for the investigation were assured if the coöperation of the British authorities could be obtained. This coöperation was secured in large part through the members of the Medical Investigation Committee of the B. E. F., of which committee Sir William Leishman is chairman. The Commander in Chief of the A. E. F. gave his permission to have experiments made on volunteers from the American Army, provided, as Col. Ireland had outlined in a communication to General Bradley, Chief Surgeon, A. E. F., that each volunteer received a careful explanation of the investigation and after this explanation signed a paper that he was willing to undergo the experiments. One of us was asked to take charge of the investigation, plan the same, select the personnel and begin work as soon as possible. The Field Marshal, Commander in Chief of the British Armies in France, gave his consent to the conduct of this work in one of the British Stationary Hospitals near the front, and the work was immediately begun.

The subjects studied experimentally have been (1) the infectivity of the blood and of its component parts, and (2) the method of transmission of the disease. These experiments have been carried out on 68 volunteers from the United States Army. All of the subjects prior to the beginning of the experiments were under observation and were known to be healthy men. Careful physical examinations of them were made. Clinical laboratory examinations were made of their blood, urine and feces, and four-hourly charts of their temperatures were kept during from one to several weeks before the experiments were begun.

Thirty-four men have been used in the blood-inoculation experiments and have been inoculated with blood or some component part of it taken from trench-fever cases in the febrile stages of the

disease. Of these, 23 have developed typical trench fever. Sixteen of them have been inoculated with whole blood, of which 15 have developed the disease. The number of individuals inoculated with the whole blood may seem large, but it should be noted in this connection that it was necessary in every series of experiments to determine the presence of the virulent organism in the trench-fever blood employed. Unless its presence could be demonstrated in the whole blood used, no conclusions could be drawn regarding its apparent absence in any part of the blood or filtrates of it.

Five individuals were inoculated with clear unfiltered plasma of the blood, free from cells, all of whom have contracted the disease; 4 were inoculated with washed corpuscles, of whom 3 have developed trench fever; 5 have been injected with plasma or serum filtered through Berkefeld filters, of which none has contracted the disease; and 2 with extracts of ground corpuscles, filtered through Berkefeld filters, of whom none has contracted the disease. From these experiments it is evident that the organism causing the disease is present in the blood. It is also evident that it may be thrown down with the corpuscles of the blood by centrifugalization and is not washed free from them by saline solution; perhaps, indeed, it adheres to them in sufficient numbers to produce the disease after inoculation of the corpuscles. The organism is also probably removed from the serum with the fibrin network of the blood clot when the clotted blood is centrifugalized. The organism has not been present in the filtrates in sufficient amount or in a sufficiently virulent state to produce the disease following inoculation. If being present it remains behind on the filter, it is doubtless of sufficient size to be visible with the microscope under certain conditions or during some stage of its life history.

The incubation period of the disease produced by inoculation with blood varies from five to twenty days. Of 20 cases inoculated with whole blood or plasma, in 9 cases it was five days; in 4 cases six days; in 2 cases seven days; in 2 cases thirteen days; in 1 case nineteen days; and in 1 case twenty days. In those cases (with one exception) in which the incubation period was long (2 cases of thirteen days and 1 of twenty days) the individuals were inoculated with blood either taken late in the disease (sixth or seventh day)

or during the relapse of the fever. The blood appears from the experiments to be most infectious on the first and second days of the disease and more infectious in the first attack than during the relapse. In the first series of inoculations the blood was taken from 7 cases of trench fever occurring naturally in members of the B. E. F. and was injected from each case into a single volunteer. All of the 7 volunteers developed the disease. The organism causing the disease furthermore has been carried from 3 trench-fever cases through three successive subinoculations from the original case. In the inoculation experiments varying susceptibility to the disease, doubtless due to relative immunity of some individuals, is demonstrated by the length of the incubation period, the severity of the attack and even in one instance (so far) by failure to develop trench fever. In these instances by parallel experiments it was shown that the organism was at the time alive and sufficiently virulent in the blood to infect other individuals in a shorter time.

From a study of the temperature charts of those who have developed the disease the possibility suggests itself that the disease is caused by a protozoan organism undergoing a life cycle of about five to seven days.

To determine the natural method of transmission of the disease, 25 men have been subjected to experiment. Of these 22 have harbored lice which have bitten trench-fever cases in the febrile stages of the disease and the remainder have harbored, for the same period of time normal, uninfected lice which have not bitten trench-fever cases. In the great majority of experiments the lice were hatched from ova brought from England.

The method of infection has been briefly and approximately as follows: Three groups, in general of from 50 to 100 adult lice each, have been placed on the trench-fever cases as follows:

Group 1. Feeding occurred during the first and second days of the fever.

Group 2. Feeding occurred from the third to the sixth day of the fever.

Group 3. Feeding occurred during the first week of the disease.

Lice removed from the patient with trench fever were placed upon a volunteer. In one series of experiments all remained upon

the volunteer until he contracted trench fever, that is, for a period of thirty days. In a second series of experiments one-half of the lice were removed from the volunteer after they had been upon him for from forty-eight to sixty hours and were then placed upon a second volunteer to remain until he had developed trench fever, or if he did not develop trench fever for a period of thirty days. This second series of experiments have been performed in order to avoid direct mechanical transmission of the organism by the louse.

In another series of experiments the interval between the biting of the infected patient and the biting of the second volunteer has been extended to six days.

In still another series of experiments comprising three volunteers, so-called wild lice were employed for infection, that is, lice taken from the clothing of trench-fever cases. A fourth series of experiments is being performed to determine if the organism infects the ova of the infected louse, that is, if transmission is hereditary.

In the majority of the experiments the lice have been placed in a covered cell made of calico, strapped upon the arm with adhesive plaster. Into this cell is placed a small piece of undershirting. The cell measures from 4 inches to 6 inches by about $2\frac{1}{2}$ inches wide. In it the lice live naturally, clinging to the fibrous cloth, at other times wandering to the skin, feeding naturally upon the blood and defecating upon the skin. They also breed and lay ova; some of the latter hatch in the cell. At intervals the cell is removed, the lice are examined and the patient is allowed to scratch the area if he so desires. In this way feces may enter slight abrasions caused by the scratching. Occasionally a crushed louse is found in the cell, for the patient may often scratch himself with the cell on the arm. In other words, if the individuals contract the disease in this manner from the louse it is evidently a natural mode of infection. So far 14 of 22 who have harbored the infected lice in the manner described have contracted the disease. Eight volunteers living under exactly the same conditions and in the same compartment with those contracting trench fever, but kept free from lice, have remained healthy. The four controls bitten by normal uninfected lice have all remained healthy. The period from the date the lice were placed on the patient to the time the disease began has been in 1 case sixteen

days; in 2 cases nineteen days; in 3 cases twenty days; in 2 cases twenty-five days; in 3 cases twenty-six days; and in 1 case thirty-one days. Here again we have perhaps evidence of a life cycle of five to seven days, the disease developing definitely at the time of the beginning or ending of a life cycle of the parasite. The time of development of the disease, as might be expected, is somewhat longer than in the majority of the cases in which the disease was produced by the injection of a large dose (10 c.c.) of the blood, though in two instances, as noted, the individual inoculated with whole blood did not develop the disease until the twentieth day after inoculation.

The type of disease produced by inoculation of the blood and by the louse infection is apparently the same. The lice employed to infect five volunteers, Nos. 23, 9, 17, 28 and 52, who developed the disease were allowed to feed first upon 5 trench-fever cases and were then placed upon five volunteers, Nos. 5, 39, 42, 47 and 13 respectively for forty-eight to sixty hours. One-half of these lice were then removed and placed upon Nos. 23, 9, 14, 28 and 52, of whom all developed the disease later. Apparently, therefore, the transmission of the disease is not necessarily direct and mechanical.

The cases of experimentally produced trench fever have been seen and the diagnosis of the disease confirmed not only by all the members of the American Committee but also by the members of the Trench-fever Commission of the B. E. F., consisting of Sir William Leishman, Chairman, Major-General Sir Wilmot Herringtham, Major-General Sir John Rose Bradford and Colonel Beveridge, as well as by a number of other prominent clinicians.

CONCERNING THROMBOSIS OF THE CORONARY ARTERIES

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Six years ago I read a paper before the Association of American Physicians on "Certain Clinical Features of Sudden Obstruction of the Coronary Arteries."[1] In that paper attention was called to the fact that while such obstruction as by a thrombus was very often suddenly fatal, it was not necessarily so, for the coronary arteries were not in the strictest sense terminal arteries; there were often anastomoses capable of reëstablishing circulation in the infarcted area to such an extent as to enable the heart to functionate for a time at least. This had been shown by anatomical study of the coronaries, by necropsy observations by the pathologists, by experimental ligation of these vessels and by clinical experience controlled by postmortem examinations.

A tentative grouping of the case of coronary thrombosis based on clinical symptoms was made: (1) Cases of instantaneous death. (2) Cases of death within a few minutes or a few hours after the obstruction. (3) Cases of severity but where death is delayed for several hours, days or months or where recovery occurs. (4) A group that may be assumed to exist, embracing cases with mild symptoms—*e. g.*, a slight precordial pain—ordinarily not recognized, due to obstruction in the smallest branches of the arteries. Group 3 was the one whose clinical phenomena were discussed, as illustrative of which a few cases were briefly cited, including one with autopsy findings.

[1] Jour. Am. Med. Assn., December 7, 1912, p. 2015.

These cases of coronary thrombosis are, as it seems to me, of commoner occurrence than is generally supposed, and that is the justification for repeating some of what was contained in the former paper, for adding reports of other cases and for touching upon some recent experimental work that has a direct bearing on this subject.

Clinical Symptoms. Most of the patients are middle-aged or elderly men. The heart and bloodvessels in many show the evidences of arterial and cardiac sclerosis; the blood-pressure may be high. In others no sign of such change is to be made out. In fact, in my 3 cases with autopsy the only significant vascular sclerosis was in the coronary arteries; the hearts were of normal size and there had been no hypertension during life. Previous attacks of angina pectoris may or may not have been experienced. If so, the patient will describe the attack due to the coronary thrombosis as of unusual severity. Often there is no assignable cause for the attack, such as is commonly noted in the typical paroxysmal angina—walking, a heavy meal, undue excitement, etc., though in some cases these exciting factors seem to provoke the attack or at least greatly to aggravate it when it has started. The painful seizure is usually more enduring than in ordinary angina, the spell lasting many minutes or several hours or a status anginosus developing. The location of the pain, as in the classical angina, is commonly substernal with frequent radiation to the arms and neck. But in many of the thrombotic cases the pain is beneath the lower sternum or even in the upper epigastric region, and there may be no radiation to the arm or neck. This epigastric reference of the pain with the nausea and vomiting that frequently occur often suggests to patient and physician some abdominal accident, such as acute pancreatitis, perforation of the gall-bladder or of a gastric or duodenal ulcer. And these suspicions are strengthened by the fact that there are so frequently signs of shock and collapse—ashy hue of the face, clammy skin, small, rapid, feeble pulse.

The heart is commonly rapid even to 140 or more, though slow heart action has been recorded. There may be irregularities such as extrasystoles or partial block. The pulse usually lacks in strength, may be almost imperceptible, though in some cases the strength is wonderfully well preserved. Blood-pressure is lowered and tends

to grow lower in the unfavorable cases. The heart tones may be startlingly faint both because of the weakness of the heart's musculature as well as because of an acute emphysema that may develop and mask the heart sounds. Over the infarcted area a pericardial friction is sometimes heard. The heart may reveal evidence of dilatation by its increased area of dulness and its mitral systolic murmur, due to relative insufficiency of the valve. Rales in the bronchi with other evidence of pulmonary edema may be present. Passive congestion of the kidney may show in a trace of albumin in the urine. In some cases cardiac edema of marked degree appears, the albumin being large in amount, the legs badly swollen and free fluid present in the abdominal cavity. The mind is commonly quite clear. I have been surprised at the preservation of bodily strength that is often manifested. Patients occasionally walk about within a few hours after such a seizure and within a few days may be out of doors trying to attend to business.

These symptoms will often enable one to make a reasonably certain diagnosis of acute obstruction of the coronary artery. As in so many other conditions the first essential is to think of this condition as a possibility and to rid the mind of the notion that such a diagnosis is only possible at autopsy.

In the following 3 cases the diagnosis was confirmed by autopsy. In the first instance, the first I had ever recognized clinically, the diagnosis was decidedly tentative and hesitating. In the other two, as well as in several in which no autopsy has been permitted or in which the patients are still living, diagnosis has seemed definite, as clear, for instance, as in most cases of obstruction of a cerebral vessel. I give very brief abstracts: Case I is reported more in detail in the article of six years ago.

Case I.—A man, aged fifty-five years, was seized with severe pain low in the chest and epigastrium. He vomited. The physician, believing, as did the patient, that the attack was of gastric origin, washed out the stomach, but relief came only with morphin. The man lived fifty-two hours. He was conscious to the last. His pulse from the first was rapid and very weak, the heart tones nearly inaudible. An acute emphysema with many moist rales developed. The temperature never was above 99.2°. No abdominal or other cause than cardiac could be made out as an explana-

tion for the condition. The left ramus descendens was found plugged by a thrombus at a narrow spot, where there was a small pathological mural roughening and thickening.

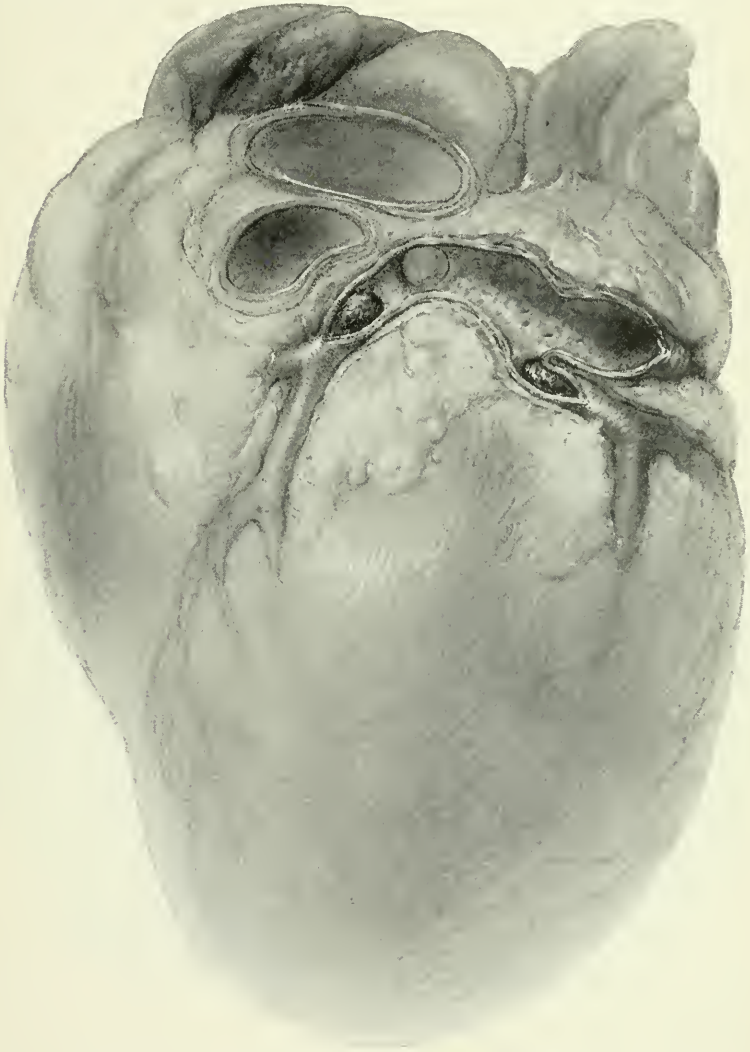

FIG. 1.—Showing site of thrombi and fairly normal external appearance of the heart.

CASE II.—A man, aged sixty-two years, while walking on the boardwalk at Atlantic City, was seized with a terribly severe pain in the lower pre-

cordia. He was helped to the hotel but refused to call a physician while in Atlantic City or for the next two days while in New York, for, as he said, he knew from the severity of the initial pain, the great weakness and difficult breathing, that he would be ordered to a hospital, and he wished to get to his home in Chicago for his illness and, as he feared, his death. He lived over two weeks from the onset of the attack. His heart when he reached Chicago was dilated, weak and somewhat rapid. His blood-pressure became progressively lower. There were dyspnea, cyanosis and marked edema of the legs and albuminuria. Death was as in ordinary cardiac failure. Necropsy revealed recent plugging by a thrombus of the descending branch of the left coronary, with softening of the heart muscle at the left apex and the lower interventricular septum.

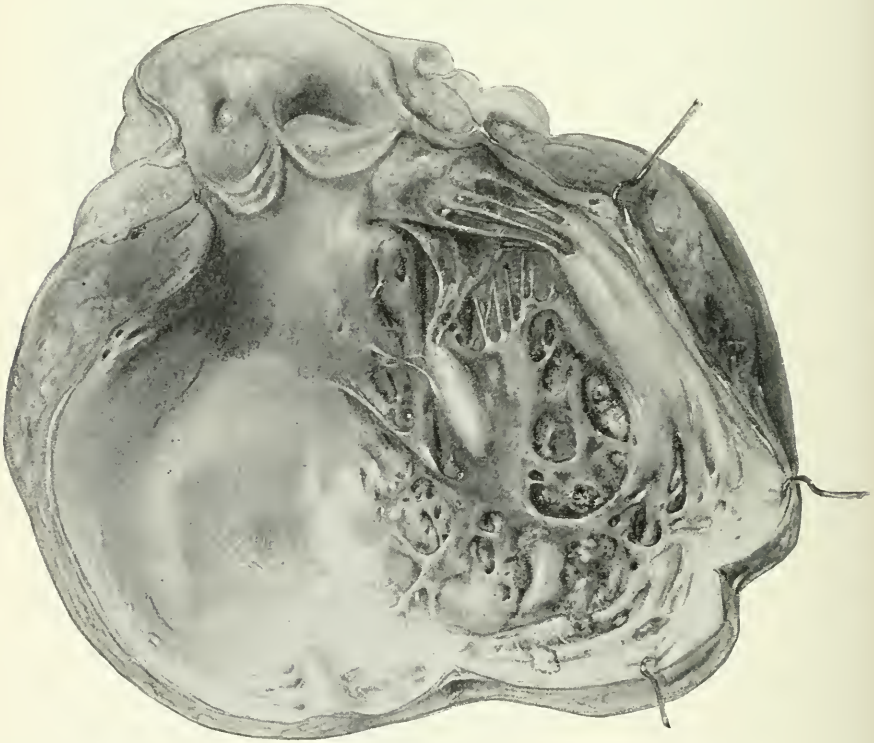

FIG. 2.—Showing changes on the endocardial surface of the left ventricle.

In this as in the other case cited the aorta was free from evidence of sclerotic change. No other vascular lesions were found than the

isolated patches of sclerosis in the coronary. It happened also that in each case the patient had only a short time before been carefully examined by competent physicians and had been pronounced in good health as to heart, blood-pressure, urine, etc.

Case III.—A physician, aged forty-two years, who had never suffered from angina pectoris, had no acute or chronic infection, so far as he knew, and who regarded himself as free from cardiovascular and renal disease, was seized while in this seemingly good health with a sudden, excruciating pain in the lower sternal region, which pain radiated to the arms and to the epigastrium. He was profoundly shocked; very weak; nauseated; the skin was cold and clammy; the pulse rapid and thready. His colleagues who saw him thought he would die in a very short time. Morphin was necessary to control the pain. After a time he rallied and in ten days was able to be about and even tried to do some professional work. But in a few days his weakness, precordial distress on exertion, dyspnea, irregular, rapid and small pulse caused him to give up. He rested, again improved and came to Chicago. He was seen by my assistants, J. R. Greer and F. M. Smith, who ventured a diagnosis of coronary obstruction, a diagnosis that I felt was correct when I saw him a few days later. Electrocardiograms taken on these two occasions gave support to these opinions, a point to which reference will be made later. Rest and small doses of digitalis were ordered and improvement followed. The summer vacation was spent on an island where there was considerable violation of the injunction as to quiet and digitalis, the patient not only eating very heartily but not infrequently going on strenuous walks, fishing and hunting trips, even though precordial pain, occasional attacks of dyspnea and cardiac irregularity gave warning that the heart was far from normal. From an unduly severe strain of this sort he suffered for several days with dyspnea and arrhythmia; he contracted an infectious bronchitis and hastened to Chicago, where, in a deplorable condition, he went under my care in the Presbyterian Hospital September 26, 1917. The dyspnea and cyanosis were marked; he was sleepless; had Cheyne-Stokes breathing and a temperature to 102°. The blood-pressure was not high, the heart was slightly enlarged to the left and there was a faint systolic murmur at the apex. After four days he developed signs of pneumonia, respiration rose to 32 and temperature to 105°; there was bloody and rusty sputum, marked albuminuria, leukocytosis; he became delirious, and just as a distinct drop in temperature and a clearing of the mind made one wonder if recovery after all might be a possibility, he died suddenly October 8, 1917. Autopsy showed pneumonia of the lower lobe of the right lung, with several infarcts. The heart was large, the left ventricle at the apex, the lower interventricular septum

and the papillary muscles, especially the anterior one, thinned, scarred and cutting like gristle. The descending branch of the left coronary and

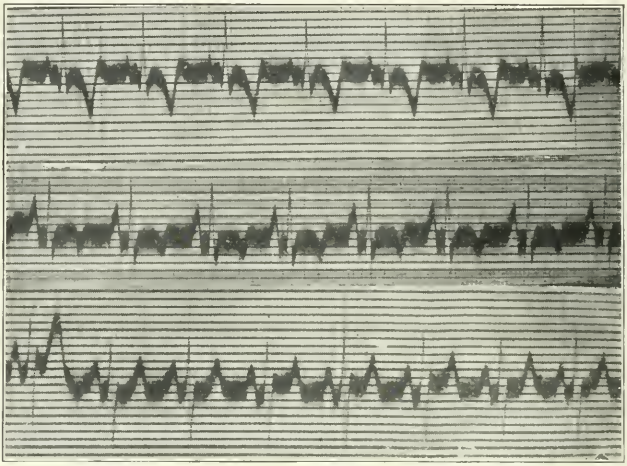

FIG. 3.—Case III. Electrocardiogram taken May 3, 1917, forty-one days after the coronary obstructive symptoms. Digitalis was not used at this time.

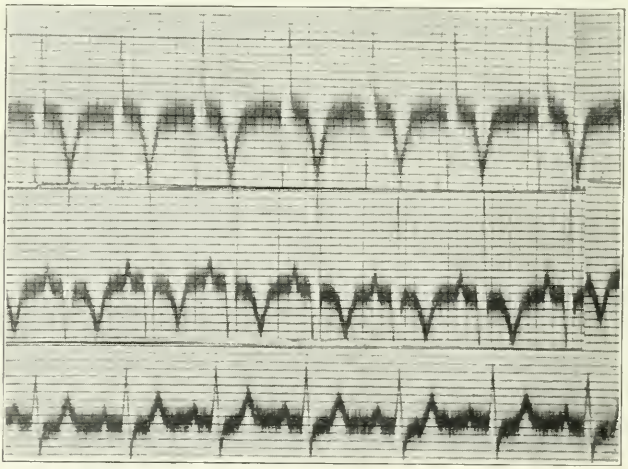

FIG. 4.—Dog. Electrocardiogram taken two days after ligation of anterior and posterior descending branches of the left circumflex artery.

the large descending branch of the left circumflex were completely obliterated by old thrombi. The only sclerotic changes in the arteries were a few

small patches in the aorta close to the openings of the coronary arteries and similar patches in the coronaries themselves. It may be added that no

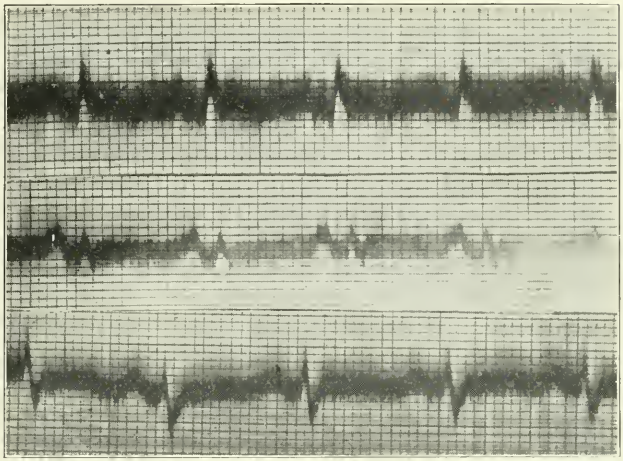

FIG. 5.—Case III. Electrocardiogram taken September 27, 1917, one hundred and seventy-eight days after the coronary thrombosis.

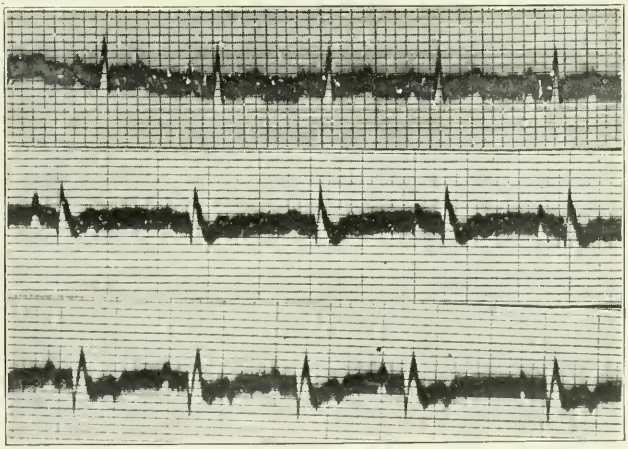

FIG. 6.—Dog. Electrocardiogram taken thirty-four days after the ligation of the ramus circumflexus sinister. Compare this low voltage tracing with Fig. 5.

history or stigmata of syphilis were noted during life and that the Wassermann test on the blood had been negative.

The following is taken from the necropsy record (Dr. Thatcher) of the Presbyterian Hospital October 8, 1917:

The heart weighs 415 gm. The enlargement involves both sides of the heart. The external surface is fairly normal in appearance, with the exception of a pale, depressed area 4 cm. in diameter midway between the base and apex of the left ventricle and a smaller similar area on the lateral surface close to the apex. The wall of the left ventricle near the apex and the interventricular septum are thin and of gristly consistence, cutting with marked resistance. The endocardium of the left ventricle has a pale, mottled appearance, especially marked over the lower three-quarters of the septum and the papillary muscles. The papillary muscles are smooth, contracted, firm, these changes being particularly marked in the anterior muscle. The greater extent of the fibrous changes in the endocardial and subendocardial tissues as compared with those on the external surface of the heart is striking. The left coronary artery contains an organized thrombus in the ramus decendens anterior 3 cm. from its origin. Also the first descending branch of the circumflex is occluded 1.5 cm. from its origin. The coronary arteries show sclerotic plaques scattered throughout most of their course, these spots varying in size from 0.5 to 2 mm. in diameter. The aortic leaflets are thickened. There are a few sclerotic areas in the suprasigmoid area of the aorta.

I wish to call attention briefly to certain experimental work that has a direct bearing on the question of obstruction of the coronary arteries. At my suggestion Dr. Fred M. Smith, in the Presbyterian Hospital and Rush Medical College, studied experimentally the coronary arteries in dogs.[1] His method was as follows: He took an electrocardiogram of each dog when under ether. Then the desired branch of the coronary artery was ligated. Following the operation, electrocardiograms were taken at intervals varying from a few minutes to many days or weeks. On all dogs that died or that were killed a postmortem was made and the gross and microscopic structure of the myocardial lesion was studied. Electrocardiograms were compared to see if there was uniformity in the tracings made after ligation of the same arteries and with the same lesions. Lastly,

[1] Smith, Fred. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med., June 15, 1918.

in human beings with symptoms suggestive of coronary thrombosis, the electrocardiograms were compared with those in dogs.

Results. The results may be summarized:

1. Dogs may live days, months or may recover after ligation of branches of the coronary arteries, even branches of considerable size. This is contrary to the findings of Cohnheim but is in accord with those of Porter, Miller and others.

2. After the ligation of special branches the lesions produced in the muscle are fairly constant. These lesions are most marked in the endo- and subendocardial tissues, *i. e.*, in the conducting region. These findings may be compared with those of Oppenheimer and Rothschild.

3. Following the ligation, numerous irregularities, such as extrasystoles, tachycardia, auricular fibrillation, auricular flutter, ventricular fibrillation, etc., may result. So far it has been impossible to predict the type of irregularity that will follow a ligation.

4. There seems to be a fairly constant variation in the electrocardiogram following the ligation of a particular branch of the coronary.

5. There is some hope that the work may assist in interpreting abnormal human electrocardiograms. The thought has been that if it can be proved that with a certain artery obstructed there is a definite lesion in the heart muscle or in the conducting system, and if with that lesion there is a definite electrocardiogram, may we not when we encounter that abnormal electrocardiogram in the human being, particularly if he has had symptoms suggestive of coronary thrombosis, be able to state with a reasonable degree of certainty that the patient has had obstruction in a particular portion of the coronary system? May it perhaps be possible to localize a lesion in the coronary system with an accuracy comparable to that with which we locate obstructive lesions in the cerebral arteries?

This work needs confirmation as to the regularity of the results obtained and especially as to the interpretation and conclusions. Confirmation from autopsies is particularly desired. Patients with this condition do not present themselves very often. A large proportion with coronary obstruction die a sudden death or are too ill to come to the office or to a hospital where they can have the

electrocardiographic tracings taken. And yet we have been able to take several suggestive tracings in patients in whom we believed these coronary thromboses have occurred, and in one of the cases, Case III, that lived five months after obstruction, the abnormal electrocardiograms gave helpful confirmatory evidence. Necropsy revealed the lesions anticipated. (See Figs. 1 to 6.)

A STUDY OF THE ENDOCARDIAL LESIONS DEVELOPING DURING PNEUMOCOCCUS INFECTION IN HORSES

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The development of the lesions of vegetative endocarditis during the process of immunizing horses for the production of therapeutic serum is of interest not only on account of its significance in interpreting some of the fundamental conditions underlying pneumococcus infection, but also in its relation to the pathology of endocarditis in general. The infectious nature of many forms of endocarditis is now generally recognized, but there is still much uncertainty regarding the etiology of many of the chronic valvular lesions which have hitherto been associated with rheumatism or chorea. The fact that recovery may follow infection of the heart valves has only very recently been accepted. Many infections of the endocardium are considered to have developed as secondary processes following previous injury of the tissues of the endocardium or valves and as a secondary localization developing in the course of infections arising in other parts of the body. Years ago Prudden[1] demonstrated experimentally the importance of injury in the development of infectious processes in the heart valves. In his experiments the valves of the heart were injured by passing an instrument into the heart through the bloodvessels. Following such an injury the bacteria injected into the blood stream localized on the valves. No such localization took place in the normal animal.

The recognition of the infectious nature of endocarditis is so recent that there are no reliable statistics to show the exact relationship of endocarditis to other diseases, but apart from rheumatism

and chorea the latest statistics show that pneumonia and sepsis, especially the puerperal form, are the diseases most commonly associated with infectious endocarditis. It is evident that bacteria may localize at the site of injury of the predisposed valve either entering the tissues of the valve from the blood stream through the ruptured endocardium or they may be carried through the blood-vessels which supply the valves from the coronary circulation. The distribution of this circulation of the valves of the heart of both man and animals has been recently very clearly demonstrated in the work of Bayne Jones.[2] Rosenow[3] has suggested that the localization of bacteria in these tissues as in other tissues of the body is due to certain qualities or affinities which are to be found only in certain strains or species such as the streptococcus or pneumococcus or during certain phases of the growth of these organisms.

For some years in my experiments with pneumococcus infections in animals I have observed lesions such as have been described by Rosenow and thus I am able to confirm his observations. But interesting as is his theoretical explanation of these lesions, this can hardly as yet be considered to have been demonstrated. The hemorrhagic lesions in my experience were due to the toxic effects of the inoculation. In the rabbit it was difficult to ascertain just how the lesions developed in the heart. In some instances the inoculation was given through the ear vein and the hemorrhagic lesions were entirely limited to the right heart, suggesting a direct action of the poison carried in the blood stream to the tissues of the heart. Rabbits died promptly after the inoculation, so that no valvular vegetations developed in this animal. In two old rabbits which had been immunized a long time I recall chronic lesions of the arteries with atheroma and calcareous deposits throughout the aorta extending into the iliac arteries.*

* These phenomena of pneumococcus infection are to be considered manifestations of the action of the pneumococcus poison and thus illustrative of the action of this poison on certain tissues of the body. The pneumococcus, like all other pathogenic bacteria, varies in its production of toxin and doubtless certain conditions, as yet unknown, are essential not only for its production by the pneumococcus but for its action on the tissue elements as well. This is true of all pathogenic bacteria and of all the known bacterial toxins. Although interesting it is indeed misleading to follow Rosenow to the point of assuming an exclusion or peculiar quality, faculty or adaptative capacity in the inciting agent as the dominant factor. In pneumococcus infection adaptation, broadly considered and not specifically limited to certain tissues,

In the light of this previous experience the occurrence of lesions of the endocardium in horses attracted my attention and led to the stuty at autopsy of seven animals immunized against types 1, 2 and 3 of the pneumococcus.

These horses were immunized by intravenous inoculation first with cultures killed at 54° C. and then subsequently with increasing doses of living culture. Two methods of immunization were used, one of which was the method of Cole[4] at the Rockefeller Hospital and the other was a method which I have used in all my experiments, namely, the inoculation of cultures grown in broth approximately eighteen hours. The blood of the animal, thus partially immunized, or of the normal animal was added to these cultures four to six hours before the culture was inoculated. The animal suffered more from this inoculation than with the method which Cole used, but endocardial lesions developed with both methods and the character of the lesions did not differ materially. The doses of these cultures which the animals were able to withstand varied greatly. In several the dose did not exceed 200 c.c., in others it reached 1200 and even 1500 c.c. Considering the size of the animal an inoculation of 200 c.c. is not a large dose, corresponding to about 0.5 c.c. in a rabbit. The potency of the serum of these animals in some instances deteriorated slightly before death, but it was evident from the potency

is one of the most important factors determining the development of infection; but localization in different tissues or organs after the development of infection elsewhere may also be determined by many conditions, such as temperature of an organ or the character of the tissues in satisfying nutritive requirements of the pneumococcus, and like conditions. The fact that the bloodvessels are especially susceptible to the action of the poisons of the pneumococci and streptococci; the fact that the blood often, better than any other tissues, satisfies the nutritive requirements of the pneumococcus and the streptococcus, as evidenced by the uncomplicated bacteremia; the fact that these nutritive conditions of the blood are often quickly exhausted by pneumococcus and to a much lesser extent by the streptococci, as evidenced by the prompt, early and often complete, or nearly complete, disappearance of the pneumococci from hemorrhagic exudative lesions—all these observations suggest that localization in pneumococcus and streptococcus infection follows the general laws of infection, adaptation of the agent and susceptibility of the host. If it were necessary to theorize concerning the localization of pneumococcus infection, it would be helpful to have an explanation of why it is that the bloodvessels of some tissues are often injured by the bacterial poison and rupture while others may escape. But still more profitable would be the results of careful investigation to determine the conditions in the tissues affecting the action of bacterial poison on the tissue elements or the nutritive conditions affecting bacterial growth, temperature, available oxygen, food elements, and so on. Progress in our knowledge of infection and in the clarity of our conceptions of infectious processes is now marked by and largely limited to the results of study along these lines.

of the serum and the length of time which the lesions must have persisted that animals with extensive endocarditis may produce serum of high therapeutic potency.

Five of the horses were immunized against Type I infection, one against Type II and one against Type III. The character of the lesions did not differ in these horses. In the first horse immunized with Type I the lesions were not marked, consisting chiefly of petechial and slightly hemorrhagic lesions of the endocardium of the ventricles and auricles and in the valves. In all the other horses the lesions were similarly distributed and occurred with all three types of the pneumococcus showing clearly that there is no essential quality or character of the strains which determined the lesions in the heart. On the contrary, it appears that conditions in the tissues of the heart locally are the dominant factors in determining the development of the lesions; that is, the heart valves were a place of least resistance to pneumococcus infection in the body. The character of the lesions was similar in the different horses and is well shown in the photograph and drawings of different stages which are to be found reproduced at the end of this paper. Practically all the lesions were attributable to the action of the bacteria and their poisons carried through the circulation of the tissues affected. No evidence of lesions developing from superficial ulceration of the endocardium was found in any of the sections. On the contrary, the earliest stage of the lesion appeared to be injury of the blood-vessels with inflammatory reaction in which active growth of the bacteria was frequently evanescent. Nevertheless, signs of marked inflammatory reaction, infiltration of the tissues and bloodvessels, and foci of necrosis were found in which pneumococci were recognized.

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2. Bayne Jones: Am. Jour. Anat., 1917, xxi, 449.
3. Rosenow: Jour. Infect. Dis., 1909, vi, 245.
4. Cole: Jour. Exp. Med., 1917, xxvi, 537.

DESCRIPTION OF PLATES

1. Photograph of the tricuspid valve, showing practically the normal condition, with the exception of a hemorrhagic lesion in one cusp.

2. Photograph of the tricuspid valve in another horse, showing the well-marked thickening of the cusps, due to successive acute and subacute inflammatory reactions, followed by permanent thickening.

3. Photograph of the aortic semilunar valves and one mitral cusp, showing more marked and acute lesions of vegetative endocarditis.

4. Drawing of a section through a hemorrhagic focus in one valve at its base. The hemorrhagic area lies in the subendocardial tissues, and is continuous with larger areas in the heart wall at the base of the valve near by. No bacteria were found in the section of this lesion and no evidence of acute inflammatory reaction. The lesions thus suggest the earliest stages.

5. Photomicrograph of a valve, showing marked thickening without any evidence of acute inflammatory reaction.

6. Photomicrograph of section through the lesions of the valves shown in the photograph (3) of the lesions in gross. The section is stained by the method of Gram and Weigert, to demonstrate bacteria and fresh fibrin. Bacteria are to be found in foci near the surface or in a few of the necrotic foci, as indicated in photomicrographs 8 and 9. The dark areas of fibrin show the patchy character of the lesion, due to the successive inflammatory reactions or to the development of new vegetations or thrombi on the valves.

7. Photomicrograph of a section through a necrotic area located under the endocardium in a connective-tissue septum of the heart wall separating the bundles of muscle fibers. The pneumococci were not in large numbers and were difficult to distinguish from the cellular necrotic and chromatin elements.

8. Photomicrograph of a bacterial focus situated near the surface of one of the vegetations.

9. Photomicrograph with higher magnification to show the pneumococci.

10. Photomicrograph of the heart muscle, showing infiltration of the tissues and an acute inflammatory focus in the center of which there is varying degrees of necrosis, such as is shown in photomicrograph 7.

11. Photomicrograph of a section through the heart walls, showing infiltration of the tissues, but especially the chronic changes in the walls of the blood-vessels.

12. Drawing under high power of the small artery shown in photomicrograph 11, which was cut longitudinally.

13. Photomicrograph of the small artery, which was cut at right angles.

14. Photomicrograph of a section of the kidney, showing the acute inflammatory reaction in this organ, described by some other observers as acute glomerulonephritis (Libman). Thickening of the bloodvessels, hemorrhagic extravasation, extreme congestion and infiltration of the adjoining tissues, such as appear in the photomicrographs and drawings of the heart wall, were also found in sections of the kidney.

15. Drawing of the congested glomeruli, degenerated tubules and infiltrated tissues shown in the center of photomicrograph 14. The distended bloodvessels near by, and also the hemorrhagic areas which were present, were not in the field which was drawn under the high power.

The accompanying heliotypes are furnished by courtesy of the Journal of Medical Research.

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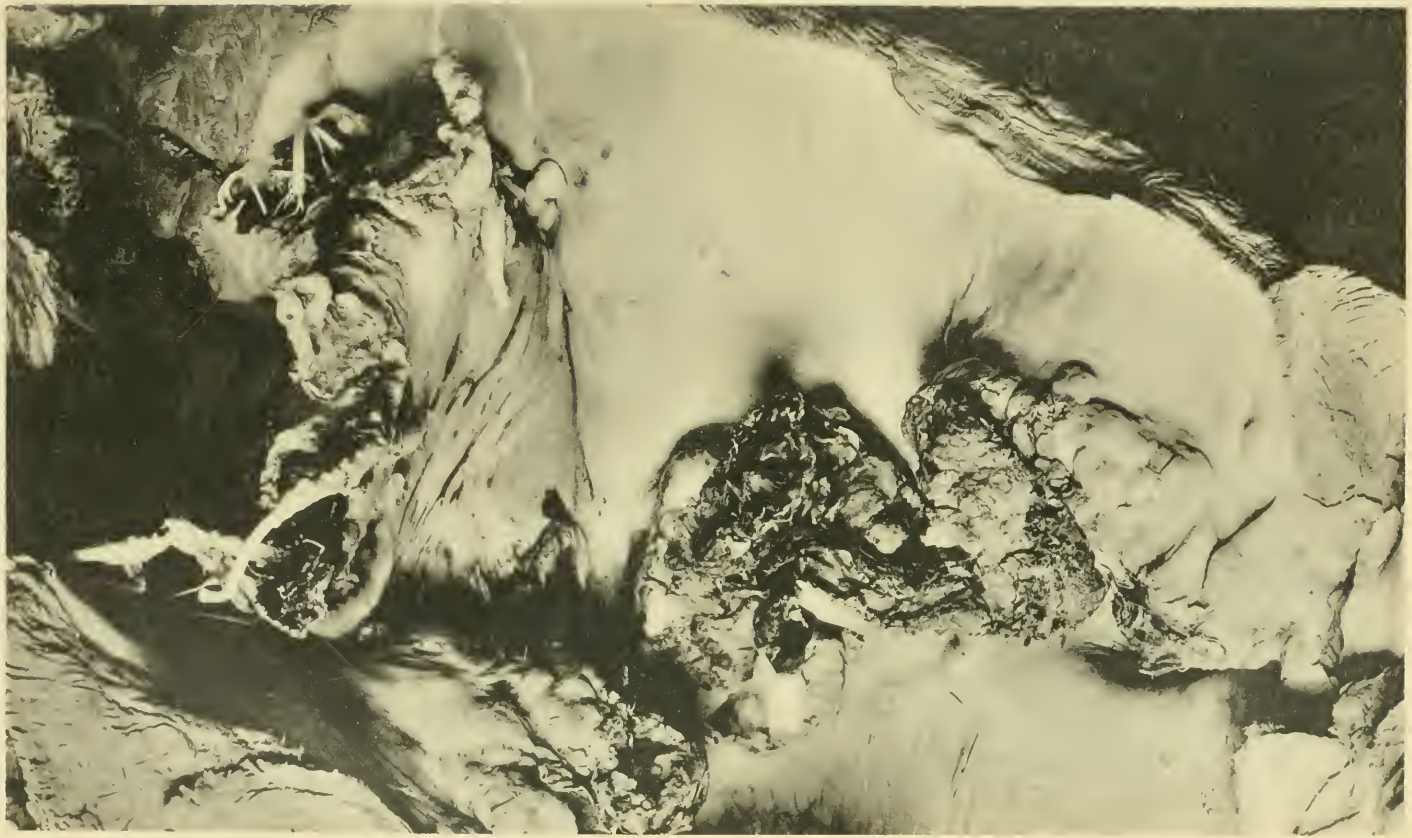

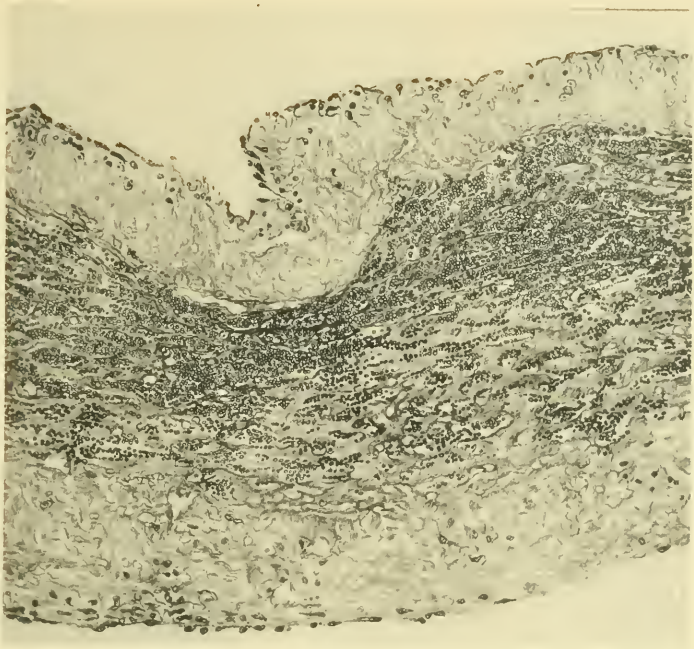

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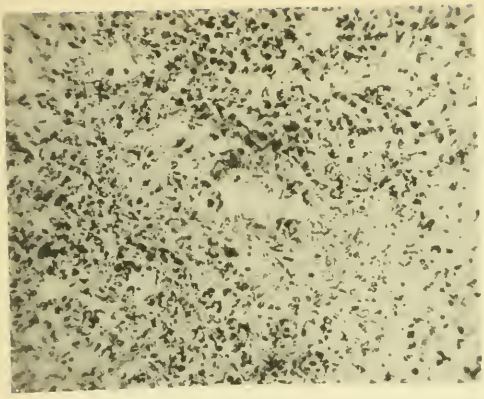

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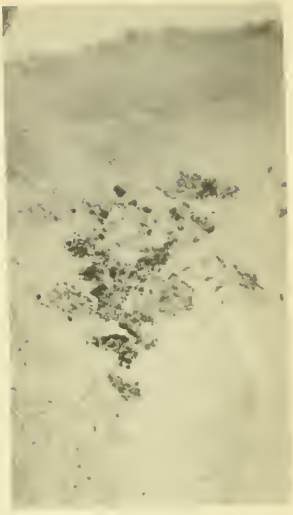

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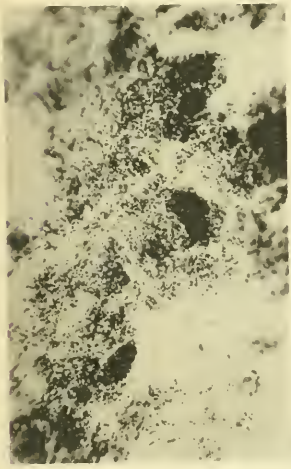

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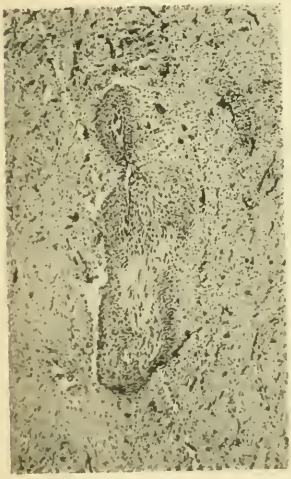

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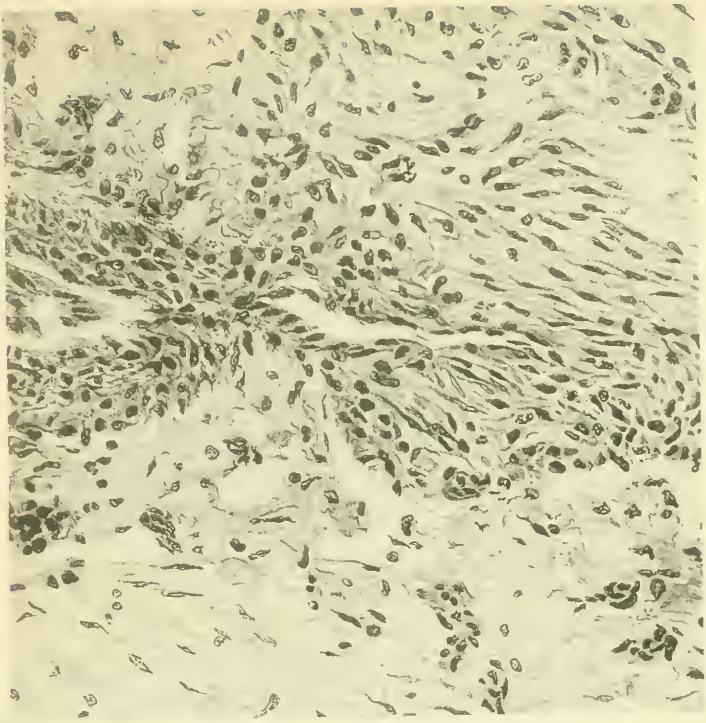

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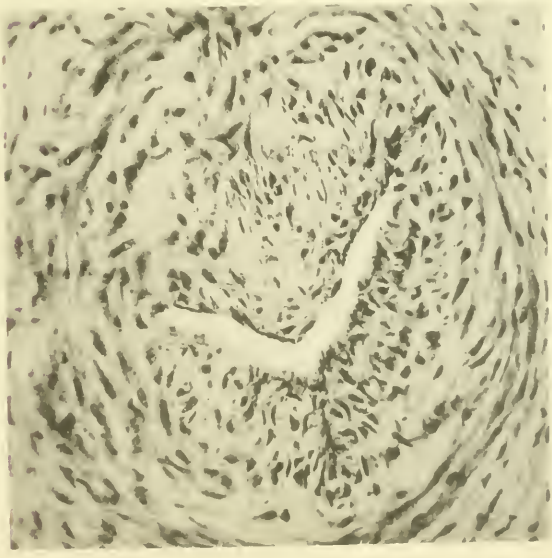

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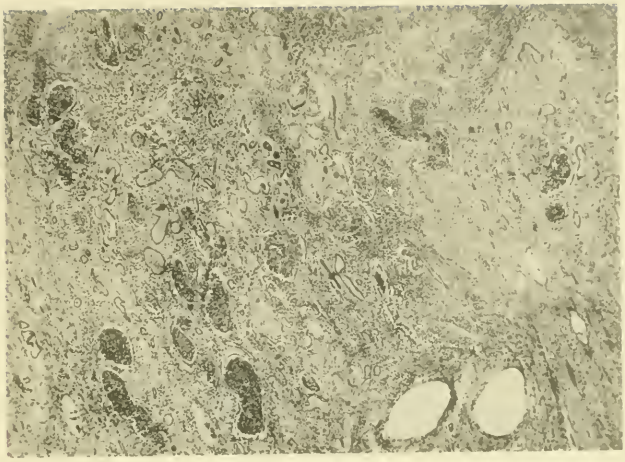

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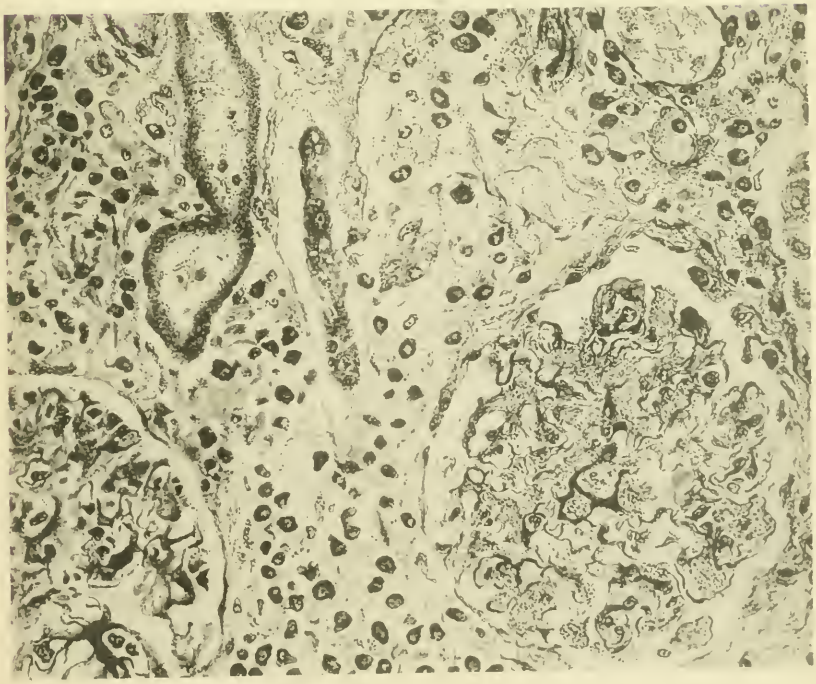

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